Record of the Respiratory Subcommittee of PTAC Meeting held on 26 August 2021

Respiratory Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Respiratory Subcommittee meeting; only the relevant portions of the meeting record relating to Respiratory Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Respiratory Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its November 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

TABLE OF CONTENTS

1. Attendance

Present

Matthew Strother (Chair)
Justin Travers
Ian Shaw
Greg Frazer
David McNamara
Stuart Dalziel
Tim Christmas

Apologies:
Neil Whittaker

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Respiratory Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

2.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

2.4. The Respiratory Subcommittee is a Subcommittee of PTAC. The Respiratory Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Respiratory Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for respiratory disease that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for respiratory disease that differ from the Respiratory Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Respiratory Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for respiratory disease.

3. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for treatment of cystic fibrosis patients aged 6 years and older with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Application

3.1. The Subcommittee noted that Pharmac sought advice from the Subcommittee regarding elexacaftor/tezacaftor/ivacaftor for the treatment of people with cystic fibrosis aged 6 years and older in the context of:

3.1.1. a supplier submission received July 2021 from Vertex Pharmaceuticals

3.1.2. correspondence and supporting evidence from Cystic Fibrosis New Zealand

3.1.3. information provided by treaters of cystic fibrosis from Pharmac's former Cystic Fibrosis Panel (disestablished 1 December 2020) to Pharmac in August 2021.

Recommendation

3.2. The Subcommittee recommended that elexacaftor/tezacaftor/ivacaftor be listed with a high priority within the context of treatment for respiratory disease subject to the following Special Authority criteria:

Initial application
Applications only from a respiratory specialist or paediatrician. Approvals valid without further renewal unless notified for applications meeting the following criteria:

1. Patient has been diagnosed with cystic fibrosis; and
2. Patient is 6 years of age or older; and
3. Either:
   - 3.1. Patient has two cystic fibrosis-causing mutations in the cystic fibrosis transmembrane regulator (CFTR) gene (one from each parental allele) (see note a); or
   - 3.2. Patient has a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis or by Macroduct sweat collection system; and
4. Either:
   - 4.1. Patient has a heterozygous or homozygous F508del mutation; or
   - 4.2. Patient has a G551D mutation or other mutation responsive in vitro to elexacaftor/tezacaftor/ivacaftor (see note b); and
5. The treatment must be the sole funded CFTR modulator therapy for this condition; and
6. Treatment with elexacaftor/tezacaftor/ivacaftor must be given concomitantly with standard therapy for this condition; and
7. Applicant has experience in the management of cystic fibrosis

Note
a) Cystic fibrosis-causing genes include F508del, G551D and other mutations listed as cystic-fibrosis causing at www.cftr2.org
b) Eligible mutations are listed on table 5 of FDA highlights of prescribing information June 2021

3.3. In making this recommendation the Subcommittee noted:

3.3.1. 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

3.3.2. 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.

3.4. 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.

Discussion

Health need

3.5. The Subcommittee noted that cystic fibrosis (CF) is a rare, genetic and progressive disease with a variable rate of progression caused by a defective CF transmembrane conductance regulator (CFTR). The Subcommittee noted that CF is characterised by multisystem organ impairment, substantial morbidity, and premature death.

3.6. The Subcommittee noted that functioning CFTR pumps chloride ions into the extracellular space, which hydrates exocrine secretions. The Subcommittee noted that a defective CFTR protein results in defective transport of chloride and other ions across the surface of epithelial cells causes a disruption in fluid homeostasis, which leads to the production and retention of thick secretions in multiple organ systems. The Subcommittee noted that the build-up of these secretions has serious clinical consequences for multiple organs including the lungs, pancreas, liver, intestine, and reproductive system.

3.7. The Subcommittee noted that the most common mutations of CFTR can be classed as deletions in the F508 gene (F), and can be classified as minimal function (MF), gating (G), residual function (RF) or other; F/F patients are homozygous for the F508del-CFTR mutation (have two copies of F508del); F/RF patients are heterozygous for F508del in the CFTR gene with a residual function (RF) mutation in the other allele; F/G patients are heterozygous for F508del in the CFTR gene with a gating (G) mutation in the other allele; F/MF patients are heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation in the other allele; F/R117H patients are heterozygous for F508del in the CFTR gene with a R117H mutation in the other allele; F/other patients 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.

3.8. The Subcommittee noted that pulmonary exacerbations, malnutrition, infections, and other complications further reduce the quality of life and life expectancy of CF patients. The Subcommittee noted that CF leads to frequent hospitalisations and is a common cause for lung transplant, and that a substantial proportion of hospital respiratory inpatient admissions are for complications of CF.

3.9. The Subcommittee noted that the CF treaters (from former CF Panel) considered that patients' day-to-day symptom burden is high and includes cough and high production of sputum, frequent infections, loss of lung function over time, as well as having to regularly take time off school or work, and that some patients are restricted to part time education or work as a result. The Subcommittee also noted that caregivers of CF patients also regularly must take time off work to support their dependents.

3.10. The Subcommittee noted that the CF treaters had considered that patients with CF have significant emotional, symptom, and treatment-related burden in day-to-day life and that the reduction in life expectancy has a significant negative impact for these patients. The Subcommittee noted that the median age of CF patients in New Zealand is 18 years while the median age of the New Zealand population is 37, and over 40% of CF patients are aged less than 16 years compared with 19% in the general population. The Subcommittee considered that this reflected the significant morbidity and mortality experienced by this patient group. The Subcommittee noted that there are approximately 540 patients with CF in New Zealand (all ages and genotypes) and noted that CF registry data available is from 2017 and does not include patients who have undergone lung transplants.

3.11. The Subcommittee noted that currently the majority of CF patients receive "best supportive care" (BSC), which includes mucolytics, osmotic agents, antibiotics, bronchodilators, enzyme and vitamin replacements and supplements, and chest physiotherapy. The Subcommittee noted that the aim of best supportive care is to slow disease progression, maintain respiratory function, improve nutritional status, improve symptoms, and enhance quality of life. The Subcommittee noted that in addition to controlling symptoms, other treatment goals include preserving lung function and improving nutritional status, reducing the rate of pulmonary exacerbations requiring antibiotics, and managing CF-related co-morbidities (eg. diabetes).

3.12. The Subcommittee noted that currently ivacaftor (IVA) is funded in New Zealand for CF-patients with specific gating (Class III) mutations but that this represents less than 10% of the New Zealand CF population. The Subcommittee noted that some of these patients will also have an F mutation and would thus be eligible for ELX/TEZ/IVA if it were funded in New Zealand under the proposed access criteria.

3.13. The Subcommittee considered that approximately 10% of the New Zealand CF population is made up of Māori and Pacific people, and that there is insufficient information to characterise these CF patients in terms of their CF mutational status. The Subcommittee considered that due to such small patient numbers, it is difficult to ascertain if Māori and Pacific patients have worse outcomes than non-Māori non-Pacific patients, but considered this likely, noting that Māori and Pacific patients suffering from other respiratory illnesses have consistently worse outcomes than non-Māori non-Pacific patients. The Subcommittee noted that the CF treaters had considered that it was highly likely that Māori and Pacific patients would have worse outcomes, given that Māori and Pacific patients suffering from other respiratory illnesses have consistently worse outcomes than non-Māori and non-Pacific patients. The Subcommittee noted that Māori and Pacific people are underrepresented in the group who may be eligible for ELX/TEZ/IVA. The Subcommittee noted that respiratory health and diabetes are described as Pharmac priority health areas of focus for Māori, however considered that CF-related bronchiectasis should not be conflated with non-CF bronchiectasis, this being a setting where Māori and Pacific people are over-represented, and that similarly CF-related diabetes should not be conflated with type 2 diabetes, where Māori and Pacific people are also overrepresented.

3.14. The Subcommittee noted that there are a number of funded treatments for CF symptoms that are not funded for non-CF counterparts, such as insulin pumps, special foods, replacement glucose meters, sterile water (for hypertonic saline nebs), azithromycin (funded for children but not adults with non-CF bronchiectasis), colistin injection, gentamicin injection, tobramycin injection, tobramycin solution for inhalation.

3.15. The Subcommittee noted that the daily treatment burden of CF is high and increases with age and disease severity. The Subcommittee noted that the CF treaters considered that daily treatment can include three to four hours of nebulised treatments, in addition to regular clinical visits with specialists, regular hospitalisations, and having to take multiple other medications daily.

3.16. The Subcommittee noted that the majority of CF patient hospital admissions are for the treatment of respiratory infections and cited a study that reported that 75% of hospitalisations were coded as respiratory-related (Stephenson et al. Pediatr Pulmonol. 2011;46:376-84), and considered that many factors may predispose some CF patients to require more frequent hospitalisations, such as: poor lung function, CF-related diabetes, poor nutritional status, poor exercise performance, *Burkholderia cepacia* infection, *Staphylococcus aureus* infection, *Pseudomonas aeruginosa* infection, *Aspergillus fumigatus* colonisation, poor medicine adherence, lower socioeconomic status, or having a high risk genotype such as F/F. The Subcommittee however considered that these factors in turn may be markers for more severe disease rather than an individual patient's predisposition to hospitalisation.

3.17. The Subcommittee considered that there is likely a high variability in patients and their health care that influences the rate of lung function decline in CF patients. The Subcommittee noted that F/RF mutations are associated with slower rates of decline over time, as is adherence and access to best supportive care. The Subcommittee also noted that pulmonary exacerbations are generally thought to contribute to faster lung function decline. The Subcommittee noted that Cogen et al. (Pediatr Pulmonol. 2015;50:763-70) reported that female gender, frequent or productive cough, low BMI, pulmonary exacerbations, and *Staphylococcus aureus* and *Stenotrophomonas maltophilia* infections caused greater lung function decline over time, while Harun et al. (Paediatr Pespir Rev. 2016;20:55-66) reported that *Pseudomonas aeruginosa* infection and pancreatic insufficiency contributed to an increased rate of lung function decline. The Subcommittee considered that there is significant uncertainty in published data regarding the above factors and that the evidence overall is inconclusive.

3.18. The Subcommittee noted that the CF treaters considered that adverse health events out of the patients control such as *Pseudomonas aeruginosa* infection or influenza can cause a more rapid decline, from which patients do not usually recover. The CF treaters considered that in general lung function decline is usually linear, but that there are clear instances where there is a stepwise drop in lung function related primarily to exacerbations, and that there is a correlation between frequency of exacerbations and the rate of lung function decline. The Subcommittee also noted that the CF treaters considered that the correlation between genotype and phenotype in CF patients is imperfect, and that two patients with the same mutations may not have the same rate of disease progression, but that in general mutational status indicative of more severe disease would almost certainly have an accelerated decline in lung function. In addition, the CF treaters considered that the rate of lung function decline was also driven by environmental factors, which would likely also be influenced by socioeconomic factors. The Subcommittee also noted that there are various other disease modifying genes known to affect CF severity and the rate of lung function decline, but that the effects of these have not been well characterised, and that testing for modifying genes is not widely available.

3.19. The Subcommittee considered that the New Zealand CF patient population would have comparable baseline characteristics to CF patients in the United Kingdom, due to the two populations being primarily Caucasian, but noted that the New

Zealand patient population is relatively uninfluenced by CFTR modulator therapies and likely have less access to CF specialist clinics than their UK counterparts, which may contribute to the reduced average age of the CF population in New Zealand compared with the United Kingdom.

3.20. The Committee considered that overall, the strength and quality of evidence relating to the high health need of CF patient is excellent, both globally and in the New Zealand context, and noted the substantial evidence supporting the health need of this patient population provided by the supplier and CFNZ.

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)

3.21. The Subcommittee noted that ELX/TEZ/IVA is a CFTR modulator with multiple modes of action; ELX and TEZ bind to different sites on normal and F508del-CFTR proteins to increase processing and trafficking to the epithelial cell surface, and IVA potentiates functioning of this CTFR protein by increasing channel gating and enhancing chloride transport.

3.22. The Subcommittee noted that there are multiple definitions of pulmonary exacerbations throughout the literature and that in some instances severe pulmonary exacerbation is sometimes defined as a pulmonary exacerbation requiring hospitalisation. The Subcommittee considered that rates of exacerbations vary by definition and that no one definition is ideal or superior. The Subcommittee considered that a decrease in exacerbations by any definition in a clinical trial likely translates to a similar decrease in exacerbations defined by a different severity or defined by different criteria (Van Devanter et al. J Cyst Fibrosis. 2021;20:39-45). The Subcommittee therefore considered that the definition of pulmonary exacerbations in the clinical trials for ELX/TEZ/IVA to be reasonable.

3.23. The Subcommittee considered that once those CF patients without eligible genotype for ELX/TEZ/IVA and those under the age of 6 years are excluded, the patient population eligible for treatment with ELX/TEZ/IVA would comprise approximately 400 patients and that it would be reasonable to assume a 3% increase for this patient population each year based on historical prevalence data, and that widespread uptake of ELX/TEZ/IVA may increase survival and hence prevalence of CF in the community over time (Cystic Fibrosis New Zealand. 2017. Data Registry. 2012 to 2017). The Subcommittee considered that most of the patients who would not be eligible for ELX/TEZ/IVA would have less severe disease.

Evidence

3.24. The Subcommittee noted several studies provided by the supplier supporting the efficacy and safety of ELX/TEZ/IVA in CF patients with homozygous or heterozygous F508del mutations:

3.24.1. Study 102 (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]): a phase III randomised, double-blind, active-controlled, parallel-group study that included 405 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). Patients were treated with either with ELX/TEZ/IVA (n=201) or placebo (n=204) over 24 weeks. At week 24, the mean absolute change in ppFEV1 between the two treatment groups from baseline was 14.3 (95% CI

12.7 to 15.8; p<0.001), and the mean absolute change in sweat chloride between the two treatment groups from baseline was -41.8 mmol/L (95% CI -44.4 to -39.3; p<0.001). Pulmonary exacerbations decreased by 63% in the ELX/TEZ/IVA treated group (rate ratio 0.37; 95% CI 0.25 to 0.55; p<0.001) and CFQ-R Respiratory Domain score increased by 20 points (least squares mean difference 20.2 between ELX/TEZ/IVA and placebo; 95% CI 17.5 to 23.0; p<0.001).

3.24.2. Study 103 (Heijerman et al. Lancet. 2019;394:1940-48): a phase III randomised, double-blind, active-controlled, parallel-group study that included 113 stable CF patients aged 12 years and older homozygous for F508del-CFTR mutation (F/F patients) with ppFEV1 between 40% and 90%. Patients were treated with either ELX/TEZ/IVA (n=56) or TEZ/IVA (n=52) over 4 weeks. At week 4, the mean absolute change in ppFEV1 between the two treatment groups from baseline was 10.0 (95% CI 7.4 to 12.6; p<0.0001) and the mean absolute change in sweat chloride between the two treatment groups from baseline was -45.1 mmol/L (95% CI -50.1 to -40.1; p<0.0001). CFQ-R Respiratory Domain score increased by 16.0 points in the ELX/TEZ/IVA treated group versus a decrease of 1.4 in the TEZ/IVA group (mean difference 17.4 between ELX/TEZ/IVA and TEZ/IVA; 95% CI 11.8 to 23.0; p<0.0001). In Study 103, the health-related quality of life improvements with ELX/TEZ/IVA over TEZ/IVA were seen in 7 of the 11 CFQ-R non-RD scores, including vitality, physical functioning, and health perceptions.

3.24.3. Study 105 (unpublished, ClinicalTrials.gov Identifier: NCT03525574): 96-week results from patients enrolled in studies 102 and 103, where all patients were treated with ELX/TEZ/IVA.

3.24.4. Study 106 part B (Zemanick et al. Am J Respir Crit Care Med. 2021;203:1522-32): a phase III 24-week open-label study that included 66 stable CF patients aged 6 to 11 years 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). Patients were treated with ELX/TEZ/IVA for 24 weeks. F/F patients had a mean absolute change from baseline in ppFEV1 of 12.2 (95% CI 7.2 to 15.2; p<0.0001), a mean absolute change in sweat chloride of -70.4 mmol/L (95% CI -75.6 to -63.3; p<0.0001), a mean absolute change from baseline in CFQ-R Respiratory Domain Score of 7.0 points (95% CI 3.9 to 10.1), and a mean absolute change from baseline in lung clearance index (LCI2.5) of -1.64 (95% CI -2.34 to -0.94). Patients with F/MF mutations had mean absolute change from baseline in ppFEV1 of 9.1 (95% CI 7.2 to 15.2; p<0.0001), a mean absolute change in sweat chloride of -55.1 mmol/L (95% CI -59.0 to -51.2; p<0.0001), a mean absolute change from baseline in CFQ-R Respiratory Domain Score of 6.9 points (95% CI 3.2 to 10.6; p=0.0005), and a mean absolute change from baseline in LCI2.5 of 1.72 (95% CI -2.11, -1.33; p<0.0001). Overall, in Study 106 the mean absolute change from baseline in ppFEV1 for all patients was 10.2 (95% CI 7.9 to 12.6; p<0.0001), the mean absolute change in sweat chloride from baseline was -60.9 mmol/L (95% CI -63.7, -58.2; p<0.0001), the mean absolute change from baseline in CFQ-R Respiratory Domain Score was 7.0 points (95% CI 4.7 to 9.2; p<0.0001), and the mean absolute change from baseline in LCI2.5 was -1.71 (95% CI -2.11 to -1.33; p<0.0001).

3.24.5. Study 116 (unpublished, ClinicalTrials.gov Identifier: NCT04353817): a phase III randomised, double-blind, active-controlled, parallel-group study that included 121 stable CF patients aged 6 to 11 years who were heterozygous

for F508del in the CFTR gene with a MF mutation (F/MF patients) treated with ELX/TEZ/IVA or placebo over 24 weeks.

3.25. The Subcommittee was made aware of the recently published Study 104 (Barry et al. N Engl J Med. 2021;385:815-25), a phase III double-blind, randomised, active-controlled trial involving 258 CF patients aged 12 years or older who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes) treated with either ELX/TEZ/IVA (n=132) or active control (either IVA or TEZ/IVA n=126) for 8 weeks.

3.25.1. Patients treated with ELZ/TEZ/IVA had a ppFEV1 mean absolute change from baseline of 3.7 (95% CI 2.8 to 4.6) compared with 0.2 in the active control group (95% CI -0.7 to 1.1; between group difference 3.5; 95% CI 2.2 to 4.7; p<0.001). The sweat chloride concentration had a mean change from baseline of -22.3 mmol/L in the ELZ/TEZ/IVA treated group (95% CI -24.5 to -20.2) compared with 0.7 mmol/L in the active control group (95% CI -1.4 to 2.8; between-group difference -23.1 mmol/L; 95% CI -26.1 to -20.1; p<0.001). The ELX/TEZ/IVA treated group achieved a mean difference of 10.3 in CFQ-R respiratory domain score (95% CI 8.0 to 12.7) compared with 1.6 in the active control group (95% CI -0.8 to 4.1; between-group difference 8.7; 95% CI 5.3 to 12.1). Subgroup analyses of patients with F/G and F/RF genotypes were consistent with the results of the primary overall group analysis.

3.26. The Subcommittee was made aware of a prospective observational study, including 245 patients aged 12 years or over with a ppFEV1 <40 who initiated ELX/TEZ/IVA from December 2019 to August 2020 in France (Burgel et al. Am J Respir Crit Care Med. 2021;204:64-73). The Subcommittee noted that the mean absolute increase in ppFEV1 was 15.1 (95% CI 13.8 to 16.4; p<0.0001). The Subcommittee also noted that the number of patients requiring long-term oxygen, non-invasive ventilation, and/or enteral tube feeding decreased by 50%, 30%, and 50%, respectively (P<0.01).

3.27. The Subcommittee also noted various ongoing trials with publications not yet available:

3.27.1. Study 109 (ClinicalTrials.gov Identifier: NCT04105972): efficacy, safety, and pharmacodynamics of ELX/TEZ/IVA in patients aged 12 years and older with CF who are homozygous for F508del.

3.28. Study 107 (ClinicalTrials.gov Identifier: NCT04183790): a roll-over study from Study 106 investigating the long-term safety, tolerability, efficacy, and pharmacodynamics of ELX/TEZ/IVA in patients with CF aged between 6 and 11 years. The Subcommittee noted an indirect comparison of ELX/TEZ/IVA against placebo, lumacaftor (LUM)/IVA and TEZ/IVA and IVA alone submitted by the supplier. The Subcommittee considered that it was an appropriately designed network meta-analysis that included consistent trial designs and study populations (limited to those aged 12 and over) for comparison, large effect sizes, consistent results across outcome measures, and evidence of a dose response that indicated that triple therapy (ELX/TEZ/IVA) was more effective than double or single therapies, which were in turn more effective than best supportive care.

3.29. The Subcommittee noted that improvements in nutritional status and BMI were observed in all studies. The Subcommittee also noted that the expected decline in lung function in CF patients (as measured by ppFEV1) over time was not observed in these studies, and instead patients' lung function improved rapidly, with a

subsequent plateau. The Committee considered that if these results are maintained long-term, that this is evidence for ELX/TEZ/IVA protecting lung function over time. The Subcommittee considered that it could also be reasonably inferred that the lung function protection from ELX/TEZ/IVA could also extend to other organs affected by CF.

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.

3.31. The Subcommittee considered that the difference in expected benefit for ELX/TEZ/IVA in terms of ppFEV1 improvement between the 6-11 and 12+ year age groups was largely the result of a ceiling effect, and noted that younger patients with less severe disease experienced a reduced improvement in absolute ppFEV1 but that the benefit for this patient groups was nonetheless just as meaningful, as these patients actually got closer to experiencing normal ppFEV1 on treatment than the older patients with more advanced disease. The Subcommittee considered that given the baseline ppFEV1 for patients in in Study 106 (89%), compared with 61-68%, the improvements in ppFEV1 in the younger age group were as impressive when baseline lung function was accounted for.

3.32. The Subcommittee noted that the benefits and risks of ELX/TEZ/IVA do not differ between those aged 6 to 11 years and those aged 12 and over but noted that younger age groups have less severe lung damage as this has not yet had time to develop. The Subcommittee noted that despite having less lung damage the 6–11-year age group experienced significant improvements in ppFEV1, but that their CFQ-R scores did not improve as substantially. The Subcommittee considered that this was likely due to the younger age group having less severe disease, and thus better respiratory-related quality of life at baseline.

3.33. The Subcommittee noted that many patients in the studies experienced a week or two long ‘purge’ upon initiation of treatment due to the clearing of mucus from the lungs resulting from treatment with ELX/TEZ/IVA. The Subcommittee noted that 1-2% of patients in the trials discontinued ELX/TEZ/IVA due to intolerance.

3.34. The Subcommittee noted that treatment related adverse events were consistent throughout studies and across subgroups. The Subcommittee considered that methods for recording adverse events may not have been sufficiently sensitive to detect rare or slow-to-develop adverse events, and thus there remains significant uncertainty about the nature, severity, frequency or extent of the risks associated with this ELX/TEZ/IVA. The Subcommittee noted that common drug-related adverse included cough, elevated liver enzymes, rash, and mild rises in creatine kinase. The Subcommittee noted that, usually, cough, skin rash and elevations of liver enzymes were of short duration and could be managed by drug dose changes or interruptions, and that female patients, particularly those on combined oral contraceptives, may be more likely to develop a rash.

3.35. The Subcommittee noted that mild increases in blood-pressure were also reported, but considered that this is of unknown clinical significance. The Subcommittee however considered that if this medication allows CF patients to live longer, then prevention of age-related conditions such as coronary artery disease or stroke may

become more important. The Subcommittee noted that eye-problems have been reported in other studies involving IVA, but that the ELX/TEZ/IVA studies were not well set up to detect these. The Subcommittee also noted that there are post marketing reports of 7 patients who had testicular pain in the first week of drug initiation, but that this could reasonably be expected with hydration of the lumen of an obstructed vas deferens (Rotolo et al. J Cyst Fibros. 2020;19:e39-41). Overall, the Subcommittee considered that there is significant uncertainty in evaluating the risks, particularly long-term risks, until long term safety studies and real-world clinical cohort follow up studies have been completed.

3.36. The Subcommittee considered that the evidence indicates that ELX/TEZ/IVA provides patients with substantial improvements in quality life and an expectation of substantial prolongation of life; and that the medication can significantly improve sweat chloride measurements, often to the normal range, which is the best available surrogate marker for CFTR function in the internal organs. The Subcommittee considered that good efficacy of ELX/TEZ/IVA has been observed across subgroups including with different genotypes, and that results supporting a clinical benefit of ELX/TEZ/IVA have been consistent between randomised controlled trials, in before-and after analyses in open label efficacy studies and in real world cohorts. The Subcommittee considered that results were durable between timepoints within randomised controlled trials or open label extension studies.

3.37. The Subcommittee considered that the randomised controlled trials employed appropriate methods for statistical analysis, choice of control intervention, randomisation, allocation, blinding and were well matched at baseline, and that although study participant numbers were relatively small that these were appropriate and sufficiently powered given the large effect size of the ELX/TEZ/IVA. The Subcommittee also considered that the outcome variables measured were generally appropriate and that future trials could attempt to measure patient-centred outcome variables and quality of life more directly. The Subcommittee considered that given the biological plausibility, improvement in sweat chloride and ppFEV1, that it is likely that any study reporting patient-centred outcome measures will also show positive results.

3.38. The Subcommittee noted that there were many demographics not included in the clinical trials; those taking prohibited concomitant medications, pregnant individuals, people with organ transplants, patients with cancer, patients with alcohol or drug use, those with comorbidities, and those with certain infections. The Subcommittee considered that exclusion of these patients may limit the generalisability of the results to the real-world context, as many CF patients will experience one or more of the factors listed.

General comments

3.39. The Subcommittee considered that treatment with ELX/TEZ/IVA could allow patients with CF to live a nearly normal life, but also considered that a number of patients living in New Zealand already have structural lung, pancreatic and other organ damage that would not be undone by correcting CFTR activity with ELX/TEZ/IVA, and these patients would have to remain on a variety of other medications. The Subcommittee considered that ELX/TEZ/IVA is a paradigm-shifting treatment for patients with CF, in that it treats the cause of CF rather than its symptoms.

3.40. The Subcommittee noted that the CFQ-R respiratory domain measure is a well validated tool and the most commonly used measure of respiratory-related quality of life in cystic fibrosis trials. The Subcommittee considered, however, that it may not capture the full multidimensional impact of cystic fibrosis on quality of life. The Subcommittee considered that it is difficult to translate changes in CFQ-R to quality adjusted life years, but that it could reasonably serve as a surrogate measure. The Subcommittee considered that there is some uncertainty surrounding a minimally clinically important difference (MCID) in CFQ-R but noted that the reported change in CFQ-R for patients receiving ELX/TEZ/IVA was clinically meaningful well beyond the MCID. The Subcommittee noted that other CFQ dimensions reported in ELX/TEZ/IVA studies have also signalled benefits, with the exception of digestive health.

3.41. The Subcommittee noted that LCI was used as an endpoint in the trials for patients aged 6-11 years. The Subcommittee noted that LCI measures heterogeneity of ventilation, whereas ppFEV1 measures large airway calibre, and that the two measures provide different and independent ways to measure lung function. However, the Subcommittee considered that they will correlate somewhat with each other to some degree, as they both evaluate lung function. The Subcommittee noted that in younger patients with early disease, ppFEV1 may be nearly normal, and that LCI is a sensitive marker of lung disease and is more likely to be abnormal for patients with CF in this age group. The Subcommittee considered that LCI may be a more responsive measure of treatment effect in this age group, as it can be difficult for younger patients to perform spirometry reliably for ppFEV1. The Subcommittee noted that there is no readily agreed upon MCID for LCI, but considered that the reported improvements in LCI with ELX/TEZ/IVA (eg. 1.7 units in study 106 and 2.2 units in study 116) indicate a significant effect size. The Subcommittee noted that LCI is not readily available as a clinical measurement in New Zealand, and therefore it would not be appropriate to include in any eligibility criteria for this patient group.

3.42. The Subcommittee noted that, like ppFEV1, worsening LCI correlates with exacerbations, worse quality of life and prognosis, and considered that it is an appropriate measure of lung function for use in clinical trials, particularly in the paediatric age group. The Subcommittee considered that both LCI and ppFEV1 are measures of lung function and probably reflect a combination of thick secretions in the airway and airway wall inflammation, but that neither correlates perfectly with quality of life or patient-centred outcomes such as being able to live independently, work, form adult relationships, or having the ability to carry out everyday tasks. The Subcommittee considered that no readily measurable outcome variable can encompass the multiple dimensions that contribute to CF morbidity, disease progression and risk.

3.43. The Subcommittee considered that there is a small proportion of CF patients for whom ELX/TEZ/IVA would be less effective, namely: those patients with genetic mutations unresponsive in vitro (these patients are not included in considerations for this application), those intolerant to ELX/TEZ/IVA, those with gating mutations who are well treated with IVA alone, those for whom ELX/TEZ/IVA may be contraindicated due to morbidity (such as severe baseline liver disease, or concomitant use of strong CYP3A inhibitors or inducers), and those with qualifying genetic mutations who may have less severe disease. The Subcommittee noted that the latter are sometimes referred to as patients with CFTR-related disorder or CFTR-related metabolic syndrome. The Subcommittee noted that patients with these conditions may have one F mutation and another that is unknown but that they should not have received a diagnosis of cystic fibrosis. The Subcommittee

considered that as a result, approximately 10% of CF patients in New Zealand would not be eligible for ELX/TEZ/IVA.

3.44. The Subcommittee noted that there are approximately 60 patients in New Zealand with CF and no F mutation (who are not included in the patient population considered for this application), and that approximately 10 of those have a gating mutation that may be eligible for treatment with IVA. The Committee noted that, of the remainder, approximately 10 CF patients have mutations where in-vitro testing suggests that ELX/TEZ/IVA will be effective; and considered that if ELX/TEZ/IVA were funded that Pharmac may consider extending access to these patients and that it would be important for these patients to have confirmed sweat chloride levels of at least 60 mmol/L. The Subcommittee noted that this would represent a small number of CF patients in New Zealand eligible for ELX/TEZ/IVA if funded. The Subcommittee considered that it would be reasonable to infer a similar benefit from ELX/TEZ/IVA for this patient group, noting the way drug development had occurred for ELX/TEZ/IVA.

3.45. The Subcommittee considered that it was difficult to define a patient population with CF at highest risk morbidity and mortality but noted that patients with higher rates of infection and exacerbations, mutations associated with more severe disease, and ppFEV1 <40 are at the highest risk of hospitalisation, mortality, and have the poorest quality of life. The Subcommittee considered that it was similarly difficult to define a CF patient population that would benefit most from treatment with ELX/TEZ/IVA, as treatment has demonstrated substantial and similarly meaningful improvements in quality of life and symptom burden for both those with progressed disease and younger patients who have not yet developed significant organ damage or lung impairment.

3.46. The Subcommittee noted that there is currently no data regarding the dosage, efficacy and safety of ELX/TEZ/IVA for the patient population under 6 years of age, and that there is currently no evidence to suggest this group would be more or less likely to benefit than those included in current and published clinical trials. The Subcommittee considered, however, that due to the robustness of the study results across age groups to date that ELX/TEZ/IVA is likely to be as effective in this age group, causing the relatively preserved lung function of early-stage disease occurring with younger age.

3.47. The Subcommittee noted that the reduced improvements in clinical trial endpoints seen in patients with F/RF mutations in the clinical trials compared with those with other mutations was likely because F/RF mutations are usually associated with less severe disease, and that the F/RF group was compared with an active comparator in the trial, as opposed to placebo. The Subcommittee considered that, in this context, the results were similarly impressive and suggested that important clinical benefits can come from the addition of ELX to TEZ/IVA even in this less severe patient group.

3.48. The 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 reduction in pulmonary exacerbations after receiving ELX/TEZ/IVA, and that this would be to a similar extent to that observed in the 12 years and older age group.

3.49. The Subcommittee considered that if ELX/TEZ/IVA were funded, it could reasonably increase the prevalence of the disease. The Subcommittee noted that improved survival would likely lead to a higher prevalence of CF (through incident patients surviving longer), and that improved health, vitality and fertility in people

with CF may lead to an increase in children born to CF parents and so to an increased incidence and prevalence of CF in the community over time. The Subcommittee considered that at this time, there is no way to quantify to what degree this may affect patient numbers in the future.

3.50. The 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. J Drug Assess. 2021;10:62-67). 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 to be funded in New Zealand. However, the Subcommittee noted the CF treaters' consideration that overall adherence rate reduction would be driven by few patients.

3.51. The Subcommittee noted that in the French cohort described above (Burgel et al. 2021), of 53 CF patients evaluated for transplantation only 7 were transplanted or awaiting transplant, the remainder having the indication for transplant suspended following treatment induction with ELX/TEZ/IVA, and that there was a 50% reduction in the rate of lung transplants for CF patients. The Subcommittee noted that these were patients with pre-existing lung damage, and that with time it is likely that treatment with ELX/TEZ/IVA may prevent severe lung disease from developing in the first place, further reducing the need for transplant. The Subcommittee considered that there is not sufficient evidence at this time to ascertain if lung transplants for these patients would be deferred to a later time in life, or if the need would be ultimately reduced. However, the Subcommittee considered the supplier's estimate of a reduction in lung transplants of approximately 80% to be reasonable, but that this would likely occur over some time.

3.52. The Subcommittee considered that estimates of health utility correlated to clinical ppFEV1 characteristics were reasonable, however, that as this metric is respiratory disease-specific it does not capture the full multidimensional impact of cystic fibrosis on quality of life. The Subcommittee noted that lung function represents only one aspect of health and thus correlates only modestly with quality of life, and that other dimensions may be measured with the CFQ-R or exacerbation frequency. The Subcommittee considered that while it is unknown how well improvement in one measure of the CFQ-R correlates with improvement in another and the overall impact on quality of life, all measures have shown substantial mean improvement on treatment and have improved to a similar extent as lung function. The Subcommittee considered that it is reasonable to expect health utility to improve similarly. The Subcommittee also considered that CF patients may experience other significant morbidities while preserving relatively good lung function with BSC, such as pancreatic issues and morbidity associated with treatment burden, and that these are not well captured when using ppFEV1 as a means of grouping patients. The Subcommittee considered that CF patients with mild disease still experience significant CF-related morbidity and treatment burden, and considered that their health utility would be expected to be worse than with full health, even with a ppFEV1 >90%. The Subcommittee considered that it was reasonable however to relate inpatients healthcare costs to underlying lung function as a surrogate for overall wellbeing, in the absence of more detailed specific information to inform on this.

3.53. The Subcommittee considered that estimates of the health sector cost of a pulmonary exacerbation event vary markedly, and that there is likely to be significant variation in costs between patients and exacerbations at different life stages. The Subcommittee noted that a two-week hospital admission can cost up to $40,000 per patient, but that this may vary widely between health providers.

3.54. The Subcommittee noted the CF treaters' consideration that over time there would be an 80% reduction in the use of BSC. The Subcommittee noted that there are multiple clinical trials underway investigating the withdrawal of BSC from the CF treatment regimen in conjunction with ELX/TEZ/IVA treatment, however that there is limited data at this time to inform this. The Subcommittee considered that it is reasonable to assume that outpatient costs for CF patients would decrease over time with access to ELX/TEZ/IVA, noting though that monitoring, and the associated check-ups would increase with patients living longer.

3.55. The Subcommittee considered that patients may not require as frequent adjustments to their antibiotic treatment strategy as occurs with best supportive care. The Subcommittee considered that antibiotic use would decrease substantially for patients treated with ELX/TEZ/IVA, particularly intravenous and nebulised antibiotics. The Subcommittee considered that there would be a substantial reduction in the need for nebulised hypertonic saline, dornase alfa and chest physiotherapy. The Subcommittee also considered that hospitalisations would likely decrease, due to decreased frequency of pulmonary exacerbations for this patient group. The Subcommittee however considered it likely that those with CF-related diabetes and/or pancreatic insufficiency will still have these morbidities after starting treatment, but that the younger cohort without CF-related diabetes might avoid this complication by using ELX/TEZ/IVA.

3.56. The Subcommittee considered that, given the magnitude of benefit seen so far in clinical trials, it is likely that there will be significant overall survival improvement in the patients treated with ELX/TEZ/IVA. The Subcommittee noted, however, that there is not yet sufficiently long-term evidence to support this, but nonetheless considered it reasonable to infer a long-term survival benefit for this patient group.

3.57. The Subcommittee considered that of the patients who are currently taking IVA who are eligible for both IVA and ELX/TEZ/IVA (ie. those with F/gating mutations), perhaps 80% would switch to ELX/TEZ/IVA, due to the potential greater efficacy as demonstrated in Study 104. The Subcommittee noted that there are 17 patients currently on the New Zealand CF register to whom this would apply, but that some of these patients are under six years of age and would thus not be eligible for ELX/TEZ/IVA. The Subcommittee considered that the eligible CF population in New Zealand would be 388 patients, increasing to approximately 430 over five years.

3.58. The Subcommittee noted the high cost of this treatment and eligible patients would expect considerable benefit from treatment if ELX/TEZ/IVA were funded. The Subcommittee considered that this would likely affect Pharmac's ability to fund this treatment for this patient group, given that it would have a very significant impact on the Combined Pharmaceutical Budget.

3.59. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ELX/TEZ/IVA if it were to be funded in New Zealand for CF patients meeting the proposed eligibility criteria. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

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 • G551D or other mutation responsive in vitro to elexacaftor/tezacaftor/ivacaftor
Intervention	ELX/TEZ/IVA • Patients <30kg one tablet in the morning containing 50mg (ELX), 25mg (TEZ), 37.5mg (IVA) and one tablet in the evening containing 75mg (IVA). • Patients >30kg one tablet in the morning containing 100mg (ELX), 50mg (TEZ), 75mg (IVA) and one tablet in the evening containing 150mg (IVA).
Comparator(s) (NZ context)	Patients with at least one F mutation - best supportive care (BSC) Patients with a mutation responsive in vitro to elexacaftor/tezacaftor/ivacaftor – 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 overall survival.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	