Interim excerpt from the Record of the Respiratory Advisory Committee meeting held on 27 April 2022

(pending publication of the full meeting record)

Respiratory Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committee Terms of Reference July 2021.

Note that this document is **not** a complete record of the Respiratory Advisory Committee meeting; only the relevant portion of the record relating to the Respiratory Advisory Committee's discussion about the application for ELX/TEZ/IVA (Trikafta) for the treatment of cystic fibrosis is included. This document will be updated in due course.

Respiratory Advisory Committee 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.

1. The role of PTAC Advisory Committees and records of meetings

1.1. This meeting record of the Respiratory Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf.The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

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

1.3. The Respiratory Advisory Committee is a Specialist Advisory Committee. The Respiratory Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Respiratory Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for respiratory diseases 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 diseases that differ from the Respiratory Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Respiratory Advisory Committee and PTAC and any other relevant PTAC Advisory Committees when assessing applications for treatments for respiratory diseases.

2. ELX/TEZ/IVA for the treatment of people with cystic fibrosis, who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene

Interests

2.1. The Advisory Committee reported no conflicts of interest with regard to this agenda item.

Application

2.2. The Advisory Committee noted additional information received from the supplier and other clinicians in response to PTAC's November 2021 consideration of ELX/TEZ/IVA, as well as specific questions posed to the Advisory Committee from PTAC.

2.3. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

2.4. The Committee **recommended** that no changes be made to its previous recommendation, where it had recommended that ELX/TEZ/IVA be listed with a **high priority** within the context of treatment of 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 six 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 genetic mutations 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 (Trikafta) prescribing information. June 2021

2.5. In making this recommendation, the Committee noted the significant health need of people with cystic fibrosis, the strong evidence of benefit of ELX/TEZ/IVA, and the exceptionally high cost of the pharmaceutical.

Discussion

2.6. The Committee noted that it had previously reviewed an application for ELX/TEZ/IVA at its August 2021 meeting, where it was recommended for funding with a high priority for those with cystic fibrosis (CF) who were aged six years and older. The Committee noted that the application was subsequently reviewed by PTAC at its November 2021

meeting where it was recommended for funding with a medium priority for those patients aged 12 years and over, but a recommendation was deferred for those patients aged 6 to 11 years and for those with mutations for which only *in vitro* data showing responsiveness to ELX/TEZ/IVA is available, pending further data. The Committee noted that PTAC had recommended that further advice be sought from the Respiratory Advisory Committee regarding the appropriateness of inclusion of renewal (or stopping) criteria in the Special Authority criteria, and whether a phenotypic definition of CF may be a more appropriate than genotypic criteria for access.

2.7. The Committee noted that in response to PTAC's considerations and additional questions for the Respiratory Advisory Committee, the supplier has submitted to Pharmac additional information for consideration by the Respiratory Advisory Committee to consider alongside PTAC's comments. The Committee also noted that a letter was provided from two clinicians experienced in the management of CF (members of Pharmac's former CF Panel and the current CFNZ advisory panel) in response to PTAC's considerations, as well as a letter from CFNZ.

2.8. The Committee noted that since its August assessment of the application for ELX/TEZ/IVA, more data has become available:

2.8.1. Study 107: patients with CF aged 6-11 years (Ratjen et al. 2021. Journal of Cystic Fibrosis November 2021. (Supplement 2):S265)

2.8.2. Study 116: patients with CF aged 6-11 years (Mall et al. German Cystic Fibrosis Conference (DMT). 2021;Conference abstract)

2.8.3. Study 109: patients with CF aged 12 years and over (Sutharsan et al. Lancet Respir Med. 2022;10:267-77)

2.9. The Committee considered this new evidence and the evidence already assessed to be of high strength and quality, demonstrating that ELX/TEZ/IVA has a significant and consistent clinical benefit up to two years at all ages and disease stages tested, works for almost all genotypes, has a good effect size, and a wide range of benefits beyond direct measures of lung function. The Committee noted that results were consistent across multiple trials, case studies, and real-world studies, and considered that the results were robust despite the heterogeneity of CF, a disease in which positive outcomes have been very difficult to demonstrate.

Ethnic variation and phenotypic eligibility criteria

2.10. The Committee noted two publications which reported that non-F508del mutations were more common amongst non-European populations, and that there was a greater frequency of rare or unknown mutations in non-European populations (Bell et al. Lancet Respir Med. 2020;8:65-124; McGarry et al. Pediatr Pulmonol. 2021;56:1496-1503). The Committee considered that while this may be true for many ethnicities, the Committee noted the New Zealand CF PORT registry, in which the New Zealand Māori patient population have similar genotypes to the European population, with over 90% carrying a mutation shown to be responsive to ELX/TEZ/IVA. The Committee considered that extending access of ELX/TEZ/IVA to those with mutations with *in vitro* evidence would further broaden the eligible patient population and thus help address any issues of inequity in this patient group.

2.11. The Committee noted that there are two main routes to diagnosis of CF. Firstly, population-wide newborn Guthrie screening detects about 90% of cases, which the Committee considered to be a comprehensive strategy for identifying the more

common mutations. The Committee noted secondly that remaining patients who become symptomatic later in life would have phenotypic testing via a sweat chloride test in the first instance followed by genetic testing. The Committee considered that while genetic testing is relatively accessible for CF patients throughout New Zealand, sweat chloride testing accessibility is variable, and some patients may have to travel distances to access testing. The Committee considered that CF diagnosis in New Zealand is comprehensive, and that almost all patients will be included in the NZ CF registry. The Committee considered that it is unlikely that the Māori CF patient population are underrepresented, due to the breadth of newborn screening in New Zealand but considered that Māori patients living rurally may encounter barriers to accessing sweat chloride testing.

2.12. The Committee noted that PTAC had requested the Respiratory Advisory Committee's advice regarding whether a phenotypic definition of CF may be a more appropriate than genotypic criteria for access, given the desire to achieve equity within the context of potentially inequitable testing. The Committee noted that appropriate access to treatment requires both a diagnosis of CF and a reasonable likelihood of response to treatment. The Committee noted that a diagnosis of CF, as opposed to a milder condition such as CFTR-related disorder, is made by demonstrating either sweat chloride levels of greater than 60 mmol/L or two CF-causing genetic mutations in the appropriate clinical context. The Committee noted that CF-causing genetic mutations are any of approximately 300 genetic mutations such as F508del that are almost always associated with severe CFTR dysfunction, and that most are rare and represent the most severe subset of the more than 3000 genetic mutations that have been associated with abnormalities of CFTR function (www.cftr2.org). The Committee noted that people with two CF-causing genetic mutations almost always have an overt CF phenotype rather than mild disease and considered that the proposed criteria for demonstrating a CF diagnosis should therefore contain both reliable genotype and phenotype criteria, in line with current clinical practice. The Committee considered that these strict criteria reduce the risk of access being extended to those with a milder clinical phenotype or to those who may not benefit, with likelihood of response to treatment determined by whether the genotype has been shown in vivo or in vitro to respond to ELX/TEZ/IVA. The Committee noted that it was not aware of any phenotype that can predict clinical response.

2.13. The Committee considered that current diagnostic practice in New Zealand is sufficient for identification of candidates for CFTR modulator therapy, and that those with rare mutations would be captured within the treatment population if access to ELX/TEZ/IVA were expanded to include those with mutations with evidence for efficacy *in vitro.* The Committee also noted that phenotypic eligibility criteria is not utilised in other jurisdictions and considered overall that phenotypic eligibility would not address inequities, which primarily relate to access to phenotypic testing services currently.

Renewal criteria

2.14. The Committee noted PTAC's recommendation that advice be sought regarding the appropriateness of renewal criteria (or stopping) criteria for patients not benefiting from treatment with ELX/TEZ/IVA. The Committee considered that re-evaluation to confirm benefit before transitioning patients to a lifetime of treatment on ELX/TEZ/IVA would not be appropriate. The Committee considered it would be difficult to identify a group for which this could apply, as all potential response measures are somewhat variable for individuals and that renewal criteria would not be able to effectively incorporate the prevention of progression of CF versus clinical benefit from baseline, especially in younger patients or those who do not have severe disease prior to initiation of ELX/TEZ/IVA treatment.

2.15. The Committee considered that only patients with mutations which have already demonstrated responsiveness to ELX/TEZ/IVA would be eligible for treatment, and that patients who would not benefit from ELX/TEZ/IVA would not meet eligibility criteria driven by mutational status in the first place. The Committee did not recommend that renewal criteria be included in the Special Authority and considered that identifying robust starting criteria would be more appropriate.

Mutations with in vitro *evidence of efficacy*

2.16. The Committee noted that PTAC had deferred making a recommendation on ELX/TEZ/IVA for the treatment of CF patients for the wide range of mutations with *in vitro* data supporting responsiveness to ELX/TEZ/IVA (Eligible mutations are listed on table 5 of FDA. Highlights of (Trikafta) prescribing information. June 2021 and https://cftr2.org/), pending *in vivo* efficacy data supporting the efficacy of ELX/TEZ/IVA for patients with these mutations in the CFTR gene.

2.17. The Committee noted that usually there is some uncertainty with extrapolating *in vitro* data to *in vivo* efficacy but considered CFTR modulators in cystic fibrosis to be an exception to this. The Committee noted that the *in vitro* assays in this context are well validated and use a human model of bronchial epithelial cells carrying the exact CFTR mutations of interest, and correction of known and well understood CFTR mutations *in vitro* translates well to *in vivo* benefits. The Committee noted that the FDA was able to reconstruct the supplier's assumptions and results for the *in vitro* efficacy of ELX/TEZ/IVA based on raw data from the supplier, which provides added confidence (Durmowicz et al. Ann Am Thorac Soc. 2018;15:1-2). The Committee considered that there is no reason to believe that pharmacokinetics and safety profiles would be different for different mutations. The Committee noted that there is already evidence of benefit translating from *in vitro* to *in vivo* for ivacaftor for gating mutations, and for ELX/TEZ/IVA for F/any mutations.

2.18. The Committee considered that the list of mutations which are responsive to ELX/TEZ/IVA *in vitro* provided by the FDA should inform access eligibility, and that this would cover approximately 90% of the CF patient population in New Zealand.

2.19. The Committee noted that ELX/TEZ/IVA has shown robust benefits for those with F/F, F/MF, F/RF or gating, and F/any mutations from *in vitro* to *in vivo*. The Committee considered there to be no reason to assume a different response in clinical trials to other in vitro responsive mutations. The Committee considered that restricting access to patients with only *in vivo* evidence of efficacy would exclude patients with rare mutations for which ELX/TEZ/IVA has shown efficacy in vitro, and which are unlikely to be investigated via clinical trial due to the small patient populations for these rare mutations. The Committee considered that restricting access to these patients would likely result in unnecessary inequities. The Committee considered that there would be a very small number of patients who have rare mutations of unknown class, not represented on the FDA list of mutations responsive *in vitro*. The Committee considered that Pharmac's exceptional circumstances framework would provide reasonable means of access for these patients with rare mutations to trial ELX/TEZ/IVA. The Committee considered that this had been effectively achieved for access to dornase alfa previously.

2.20. The Committee considered it was important to maintain the Special Authority requirement that the clinician making the Special Authority application on behalf of the patient is experienced in the management of cystic fibrosis.

Eligibility of patients aged less than 12 years of age

2.21. The Committee noted that PTAC had deferred making a recommendation on ELX/TEZ/IVA for the treatment of patients with CF aged less than 12 years of age who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, pending the availability of further data supporting the evidence of efficacy of ELX/TEZ/IVA for patients less than 12 years of age. The Committee considered the mode of action of CFTR modulators to be independent of age and that there is no biological reason to assume that younger patients with CF would respond differently to ELX/TEZ/IVA than those aged 12 years and over. The Committee noted that recent unpublished clinical trials confirm similar efficacy in patients between 6 and 11 years of age as the 12 years and over age group. As such, the Committee considered that the totality of supportive evidence for those aged 6-11 years as equivalent to that of those aged 12+ years. The Committee considered that younger patients who have a percent predicted forced expiratory volume in one second (ppFEV1) lung function testing results perceived as clinically as being within normal range may still have clinically significant lung disease and airway disruption.

2.22. The Committee noted that there is currently no evidence available for the safety of use of ELX/TEZ/IVA in patients with CF aged less than six years, and considered that eligibility criteria should restrict access to those aged six years and over pending availability of data for younger age groups. The Committee noted that this is the current approach taken by other jurisdictions where ELX/TEZ/IVA has been made available.

2.23. The Committee noted that the unpublished results from the phase IIIb Trial 116 in F/MF patients aged 6-11 years indicate that the evidence of efficacy of ELX/TEZ/IVA is consistent with the results seen in the 12 years and older age group. The Committee noted that despite being considered to have 'normal' lung function, patients experienced a ppFEV1 improvement of 11 percentage points. The Committee considered that this is a significantly clinically meaningful improvement in lung function, especially in a population whose clinical course is that of deterioration. The Committee also noted the unpublished results from Study 107 in the 6–11-year age group with F/F or F/MF mutations and noted that results appeared similar to those reported from Study 116.

2.24. The Committee noted that CF related morbidity that occurs early in life for patients with CF cannot be reversed once established, such as short stature and CF related diabetes. The Committee considered that these ongoing morbidities, and well as overall and future quality of life, need to be taken into consideration alongside lung function (ppFEV1 and lung clearance index) when considering the benefits of early treatment with CFTR modulator therapies. The Committee considered that damage done earlier in life is substantial and therefore early treatment would be important. The Committee considered that treatment with ELX/TEZ/IVA would be associated with an initial rapid improvement and a postulated change in trajectory of the disease on treatment, suggesting that more quality adjusted life years are acquired over time on treatment irrespective of age.

2.25. The Committee noted an unpublished retrospective cohort study provided by the supplier on the use of ivacaftor in the US until 2019, which reported that long-term outcomes for patients who initiate treatment young were better than for those who initiated treatment at an older age. The Committee considered that the study was potentially confounded by general temporal improvement in best supportive care, and that patients who have access to ivacaftor may have better care generally. However, the Committee considered that the same or better results should be expected with ELX/TEZ/IVA as the available data indicates that ELX/TEZ/IVA has a greater reduction in lung function decline than ivacaftor.

Lung function decline and long-term efficacy

2.26. The Committee noted PTAC's consideration that ppFEV1 was not a sufficiently-evidenced surrogate for ongoing exacerbations when observing the published trial data, in that Study 102 provided the only published data to support a reduction in exacerbations. The Committee noted that an unpublished observational US registry study of more than 16,000 patients reported a substantial reduction in frequency of pulmonary exacerbations on treatment, and that inference of exacerbation reductions from ppFEV1 lung function measurement is not necessary. The Committee considered that lung function as measured by ppFEV1 is likely the best marker for disease stage. The Committee noted that there is individual variation in lung function testing results from test to test but considered that this is mitigated by repeat and regular testing. The Committee noted that patients with CF and advanced disease have a higher rate of pulmonary exacerbations, but also noted that lung function declines for patients with CF, even without pulmonary exacerbations. The Committee noted, however, that following an exacerbation, lung function does not usually return to the pre-exacerbation level, and that an increased rate of exacerbations accelerates the rate of lung function decline.

2.27. The Committee noted that ivacaftor is less effective than ELX/TEZ/IVA in terms of effect size, and that 2-year data for ELX/TEZ/IVA shows maintenance of ppFEV1 stability, which the Committee considered is biologically likely to continue long term to reduce or eliminate lung function decline. The Committee considered that triple therapy (ie ELX/TEZ/IVA) can be considered more effective than double or single agent therapies and that different combinations of therapies will probably be explored for rare mutations when more CFTR modulator agents become available.

2.28. The Committee noted that the reduction in ppFEV1 per annum with the current state of best supportive care is 1-3%. The Committee noted that patients treated with ELX/TEZ/IVA have a stable ppFEV1 over a 2-year period in clinical trials with nil decline in lung function and considered that the slowing in lung function decline with ELX/TEZ/IVA could be considered to be 80-100% reduction for patients treated in early-stage disease, and 50-80% reduction for those with established bronchiectasis for whom exacerbations will continue, albeit at a reduced rate. The Committee noted that patients with established disease would still experience lung function decline on treatment with ELX/TEZ/IVA but would be expected to gain non-pulmonary benefits such as psychological and gastrointestinal improvements. The Committee considered similarly that quality of life may improve significantly despite minimal change in ppFEV1 for those with very early-stage disease. The Committee considered that for those with established bronchiectasis, the rate of lung function decline with ELX/TEZ/IVA would be similar to that of patients with non-CF related bronchiectasis. The Committee considered that confining measures of health gains to only lung function would likely underestimate the effectiveness and impact on quality of life of ELX/TEZ/IVA.

Additional observational evidence supporting efficacy of ELX/TEZ/IVA

2.29. The Committee noted that the supplier had provided information regarding the first interim analysis of a 5-year ongoing post-authorisation safety study (PASS) of ELX/TEZ/IVA. The Committee considered that some of the results from the study would have been confounded by the COVID-19 pandemic preventing in-person clinical evaluations, as well as general improvements in best supportive care over time. The Committee noted that the 'real-world' non-experimental observational results reported similar efficacy to that seen in clinical trials across genotypes and considered that this was impressive as the magnitude of effects observed in clinical trial results are rarely

reproduced in real-world setting. The Committee noted that the study reported lower prevalence of airway pathogens, increases in ppFEV1 and BMI, and decreased hospitalisation, exacerbations, transplant, and death.

2.30. The Committee noted a French patient subjective survey following initiation of ELX/TEZ/IVA in people with CF and advanced lung disease (Martin et al. Respir Med Res. 2021;80:100829). The Committee noted that patients were asked their perceptions of various symptoms and morbidities while on treatment. The Committee noted that the almost all patients reported improvements in chronic cough, diabetes control, pulmonary exacerbations, appetite, and sleep quality, and a reduction in daily time spent for other treatments, chest physiotherapy, hospitalisation, and lung transplant discussions.