Record of the Respiratory Advisory Committee Meeting held on 28 August 2024

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

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

The 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees 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 Specialist Advisory Committees, 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
Betty Poot

David McNamara
Greg Frazer
Justin Travers
Matthew Dawes
Neil Whittaker
Sarah McLean-Osborn
Stuart Dalziel
Tim Christmas
Jim Bartley (Attended from 2:30pm)
Michelle Wong (Attended from 2:30pm)

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA; Trikafta) for the treatment of cystic fibrosis (CF) in children aged two to five years, within the context of treatment of respiratory disease, subject to Special Authority criteria	High Priority
• Azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of rhinitis/rhinoconjunctivitis, within the context of treatment of respiratory disease, subject to Special Authority criteria	Medium Priority
• Azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of adenoid hypertrophy	Decline
• Rituximab for the treatment of systemic sclerosis interstitial lung disease in people whose disease is not responsive or intolerant to mycophenolate mofetil, within the context of respiratory disease, subject to Special Authority criteria	High Priority
• Rituximab for the second-line treatment of connective tissue disease related interstitial lung disease, within the context of respiratory disease, subject to Special Authority criteria	High Priority
• Mepolizumab for the treatment of severe chronic rhinosinusitis with nasal polyps (CRSwNP), within the context of treatment of respiratory disease, subject to Special Authority criteria	High Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. 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) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Respiratory Advisory Committee is a Specialist Advisory Committee (SAC) of Pharmac. The Respiratory Advisory Committee and PTAC and other SACs have complementary roles, expertise, experience, and perspectives. The Respiratory Advisory Committee and other SACs may therefore, at times, make recommendations for treatments for respiratory conditions 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 conditions that differ from the Respiratory Advisory Committee's, or SACs may make recommendations that differ from other SACs'.

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

4. Welcome and introduction

4.1. The chair welcomed the Committee with a karakia followed by whakawhanaungatanga.

5. Record of the Respiratory Advisory Committee meeting held Wednesday, April 27, 2022

5.1. The Committee reviewed the record of the Respiratory Advisory Committee meeting held on Wednesday, 27 April 2022 and agreed that the record be accepted.

6. Pharmac Update

6.1. The Committee noted the Pharmac | Te Pātaka Whaioranga update.

7. Therapeutic Group and NPPA Review

Funding decisions and applications

7.1. The Committee noted the funding decisions that had been made since the previous meeting.

7.1.1. The Committee noted the decision to end the temporary funding of palivizumab.

7.1.2. The Committee noted that a new treatment, nirsevimab, had been associated with large reductions in numbers of infants with respiratory syncytial virus (RSV) requiring hospital admission (Barbas Del Buey et al. Front Public Health. 2024;12:1441786).

7.1.3. The Committee noted that in New Zealand, the greatest burden of RSV is experienced by Māori and Pacific infants with a relative risk of RSV-related hospitalisation of four and about three, respectively, for these groups compared with European or other ethnicities (as noted by PTAC in February 2022).

7.1.4. The Committee also noted suitability benefits in that nirsevimab only requires one injection for six months' prevention.

7.1.5. The Committee noted that Pharmac staff have been engaging with the supplier of nirsevimab regarding submission of a regulatory application to Medsafe and a funding application to Pharmac, to enable Pharmac to assess this treatment.

7.2. The Committee noted the outstanding funding applications in the respiratory and allergies therapeutic group that are yet to receive clinical advice or be assessed.

7.2.1. The Committee noted differences in the Special Authority criteria for respiratory treatments, specifically inconsistencies regarding who is eligible to prescribe.

7.2.2. The Committee noted that simplifying the criteria could help to reduce the burden on respiratory physicians, given that nurses review many patients with chronic respiratory diseases but are unable to prescribe treatment based on the current criteria.

7.3. The Committee noted that since that last Respiratory Advisory Committee meeting, two applications related to respiratory treatments were reviewed by PTAC.

Named Patient Pharmaceutical Assessment (NPPA)

7.4. The Committee noted the summary of NPPA applications received since the last meeting. The Committee noted some of these medicines were being considered for listing on the Pharmaceutical Schedule and/or were due to be discussed at this meeting. No other medicines were raised as options for consideration for funding on the Schedule.

7.4.1. The Committee considered that it remains appropriate that NPPA applications for Trikafta are required to show evidence that the patient's mutation has strong biological or clinical reasons to be considered Trikafta-responsive.

7.4.2. The Committee noted that evidence for Trikafta is rapidly evolving and considered that the basic principle has to be sufficient evidence of benefit given the large financial consequences associated with this treatment. The Committee noted this approach is consistent with other jurisdictions.

7.4.3. The Committee considered that it is important to keep the NPPA pathway open to assess new evidence as it evolves, which is also consistent with international processes.

Respiratory inhalers

Short-acting beta agonist (SABA) and inhaled corticosteroid/Long-acting beta agonist (ICS/LABA) usage

7.5. The Committee noted the information provided on respiratory inhalers.

7.6. The Committee considered that recommendations for Single combination ICS/LABA inhaler and Maintenance and Reliever Therapy (SMART) therapy are based on reducing exacerbations, but that people using SMART in clinical practice had higher symptom burden compared to standard groups in the clinical trials. The Committee noted that, for some people where symptoms are a major factor, but exacerbations are not, receiving traditional therapy with a regular ICS and salbutamol as needed was appropriate. The Committee noted the NZ Adolescent & Adult Asthma Guidelines recommend all people with severe asthma have treatment with a single combination ICS/LABA inhaler (SMART)

7.7. The Committee considered that salbutamol is also used in the treatment of chronic obstructive pulmonary disease (COPD), which may explain the limited reduction seen

in overall usage despite a decline in usage for the treatment of asthma. The Committee noted that salbutamol use in people under the age of 12 would continue until there is evidence of a more optimal treatment for this patient cohort.

7.8. The Committee noted that it can take ten years to change practice in terms of new treatment approaches being fully implemented for asthma and COPD, and considered that not having the combined inhaler (budesonide/eformoterol) on Practitioner's Supply Order (PSO) will contribute to slower implementation.

7.9. The Committee noted that people who present to Emergency Departments (ED) with an asthma exacerbation will be treated with oral steroids and salbutamol, which will contribute to the large numbers of salbutamol dispensings.

7.10. The Committee noted that uptake for dry powder inhalers may be impacted by people who perceive that the treatment isn't working due to the different treatment experience the inhaler provides compared to a metered dose inhaler (MDI), or incorrect inhaler technique.

Budesonide/formoterol stat dispensing

7.11. The Committee noted the letter from the Scientific Advisory Board of the Asthma and Respiratory Foundation New Zealand (ARFNZ) supporting budesonide/formoterol being placed on PSO.

7.11.1. The Committee considered that placing budesonide/formoterol on the PSO would lead to a slight increase in usage, but is unlikely to result in a considerable surge in usage. The Committee noted that being able to provide an inhaler at the point of initiating prescribing, and demonstrate correct technique, would be beneficial and is expected to enhance adherence with treatment.

7.11.2. The Committee noted that all brands of budesonide/formoterol should be placed on PSO if this were to occur, as opposed to selecting any specific brands.

7.12. The Committee noted that 20% of people with asthma were discharged from hospital without being prescribed an inhaled corticosteroid (ICS). The Committee considered that in an emergency setting, people were more likely prescribed an oral steroid and a short acting beta agonist (SABA) compared to an ICS/LABA combination.

7.13. The Committee considered that any competitive process that resulted in just one inhaler being available within a treatment class of inhalers would have implementation challenges related to people having to change between inhaler treatments.

7.14. The Committee noted that if certain brands of inhalers (eg. Vannair) are not Medsafe approved for a particular indication, this can introduce a barrier to patient care provided by nurse practitioners, who are unable to prescribe treatments for unapproved indications.

Spacers

7.15. The Committee noted the letter from the Scientific Advisory Board of ARFNZ, which supported widened access to spacers via community pharmacies.

7.16. The Committee considered that spacers should be made available via community pharmacies and that this would be cost-neutral to the combined pharmaceutical budget (CPB), due to better use of the medication leading to fewer exacerbations and less doses of reliever treatment required by each individual.

7.16.1. The Committee noted that pharmacies would provide adequate training on how to use the spacer correctly. The Committee considered that having two sizes (adult and paediatric) of spacers available would be appropriate.

7.16.2. The Committee noted that MDIs ideally need to be administered with a spacer and considered that increasing access to spacers would help improve overall adherence to treatment.

Ipratropium Inhalers

7.17. The Committee noted there remains a small clinical need for salbutamol with ipratropium bromide (Duolin), however, the Committee considered that there are several suitable funded alternatives including switching to salbutamol or ipratropium monotherapy or to a LABA/LAMA (long-acting muscarinic antagonist) combination.

7.18. The Committee considered that long-term treatment of COPD should involve a LAMA as opposed to ipratropium.

LAMA/LABA market dynamics

7.19. The Committee considered that the dispensing of LAMAs and LABA/LAMAs would continue to increase with a shift towards triple therapy expected based on the New Zealand COPD Guidelines 2021.

7.20. The Committee considered that the currently funded glycopyrronium-containing inhaler devices can be physically difficult to use. The Committee noted that a triple inhaler currently being considered by Pharmac contains this medicine and considered that there likely remains a need for single and dual inhalers containing glycopyrronium.

7.21. The Committee considered that any decision to reduce the number of inhalers within each treatment class would need to be weighed up against the commercial benefits of having more products in the market.

7.22. The Committee considered that the convenience of using one inhaler once a day would be the main driver for uptake of single triple inhalers for COPD, however, that there is no evidence of improved treatment benefit with a single triple inhaler compared to multiple inhaler therapy.

7.23. The Committee considered that long-term numbers of people requiring treatments for COPD are difficult to estimate, but that there is the potential for numbers to reduce over time due to a decrease in the rate of tobacco smoking in New Zealand.

7.24. The Committee considered that market uptake in New Zealand for triple therapy inhalers would likely follow a similar uptake pattern to the Australian market.

Biologic market dynamics

Omalizumab

7.25. The Committee considered that usage of omalizumab would continue to increase at the same rate as has occurred for the past few years.

7.26. The Committee noted that the preference would be to treat severe asthma with either mepolizumab or benralizumab, for those people who meet funding criteria. However, those who don't meet all criteria for the above medications but have elevated IgE levels would be treated with omalizumab.

7.27. The Committee noted that therapy with biologics is expected to be lifelong, however with waning efficacy there may be an unknown reduction in the number of patients remaining on these therapies.

7.28. The Committee noted that currently omalizumab is the only biologic approved for use in children down to six years of age and thus provides a treatment option for a niche group with a health need.

Benralizumab and mepolizumab

7.29. The Committee noted that Pharmac has received previous advice on proposals to remove the Asthma Control Test (ACT) score from the Special Authority (SA) criteria for benralizumab and mepolizumab for severe eosinophilic asthma.

7.29.1. The Committee noted that the inclusion of the ACT score within the SA criteria limits the number of people eligible for mepolizumab, however, considered that the score was open to interpretation based on clinician understanding of good asthma control.

7.29.2. The Committee considered that there was a difference of opinion regarding the impact of removing the ACT score from the SA criteria, with one view being that it may not substantially increase usage as the other criteria target severe disease. However, another view was that it could increase usage by more than 30%.

7.30. The Committee considered that usage of biologic treatments for asthma (including mepolizumab and benralizumab) is likely to increase, given the recent focus in the literature on concerns about the adverse effects of systemic corticosteroid exposure.

7.31. The Committee noted that Pharmac has received previous advice on proposals to reduce the blood eosinophil count in the SA criteria for benralizumab and mepolizumab.

7.31.1. The Committee considered that reducing the eosinophil count in the SA criteria would increase the number of people eligible for these biologics. The Committee considered that using eligibility data from clinical trials would suggest that reducing the eosinophil count to 300 cells/uL would lead to the potentially eligible population increasing by 70%.

7.31.2. The Committee noted that based on evidence from clinical trials the health benefit of biologic treatments for people with an eosinophil count between 300 to 500 was less than for people with an eosinophil count above 500, however, a large decrease in efficacy was not observed.

7.32. The Committee noted that the ACT score and eosinophil count criteria had different purposes in the SA criteria, with the ACT score used to assess disease severity and quality of life while the eosinophil count indicates the likely magnitude of benefit from treatment.

7.33. The Committee considered that there is little difference in preference between mepolizumab and benralizumab from a clinician perspective. However, the Committee considered that the less frequent administration of benralizumab would be appealing, especially in the context of switching between the two treatments, which it considered was likely to become an increasingly important treatment strategy.

Mucolytic Treatments

7.34. The Committee noted that the Trikafta uptake since its funding was as expected.

7.35. The Committee considered that ivacaftor usage would likely continue to decline as the number of mutations eligible for Trikafta was widened. The Committee noted that some people currently on ivacaftor who would also be eligible for Trikafta hadn't switched and considered that this would likely be due to concerns about potential impacts on behavioural change and sleep disturbances associated (albeit rarely) with Trikafta treatment. The Committee considered that over time approximately 95% of

individuals with cystic fibrosis will be receiving treatment with Trikafta with approximately 5% on ivacaftor.

7.36. The Committee noted that for patients nebulising hypertonic saline, access to 4ml single-use vials would have a suitability advantage over the currently funded 90mL bottle and would be safer in terms of reducing the risk of contamination of the solution where it is used multiple times.

Anti-fibrotic Treatments

7.37. The Committee noted these treatments are effective in connective tissue diseases and considered that there is a desire for access to be widened to many groups with progressive fibrosing interstitial lung disease (ILD), not just idiopathic pulmonary fibrosis. The Committee noted that earlier treatment is more effective as there is less permanent lung damage early in the disease process.

7.38. The Committee considered that individuals with these diseases should be under the care of a respiratory specialist, which may include nurse practitioners.

7.39. The Committee noted that the Special Authority criteria for anti-fibrotic treatments require diagnosis and treatment planning by a multidisciplinary team (MDT). The Committee noted that the frequency of multidisciplinary team meetings varied around New Zealand, with these meetings often over-subscribed, meaning effective treatment is delayed. The Committee considered that the risk of negatively impacting treatment access by including this potential barrier in the Special Authority criteria needs to be weighed up against the benefits of having the diagnosis and treatment plans determined by a MDT to help determine eligibility for funded treatment, especially with complex disease states.

7.40. The Committee noted that for people with progressive fibrosing ILDs, even in cases where the disease may have progressed more than 10% while on treatment, that treatment may still be beneficial by slowing down this progression.

Adrenaline auto-injector

7.41. The Committee noted that development of patient/provider educational material could be useful to help people to better recognise when their auto-injector is expiring and prompt individuals to seek a new prescription.

Horizon scanning

7.42. The Committee reiterated the clinical interest in treatments progressing towards submission to international regulators and funders for RSV prevention, given the high health need from this disease.

7.43. The Committee considered the following treatments to be of interest, some of which Pharmac has already received funding applications for:

- depemokimab for severe asthma
- dupilumab for a range of indications including severe asthma and eczema
- brensocatib for bronchiectasis treatment.

8. Elexacaftor/tezacaftor/ivacaftor and ivacaftor - Cystic fibrosis, aged 2 years and older, at least one mutation responsive in vitro to Trikafta

Application

8.1. The Committee reviewed the supplier application from Vertex Pharmaceuticals for elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA; Trikafta) for the treatment of cystic fibrosis in children aged two to five years who have at least one F508del mutation in the CFTR gene, G551D mutation or other mutation responsive in vitro to Trikafta.

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

Recommendation

8.3. The Committee **recommended** that elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA; Trikafta) be funded for the treatment of cystic fibrosis (CF) in children aged two to five years with a **high priority,** within the context of treatment of respiratory disease, subject to the following Special Authority criteria (amendments shown in **bold** and ~~strikethrough~~):

Initial application
Applications from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. Patient has been diagnosed with cystic fibrosis; and
2. Patient is **two** ~~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); 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); 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.

Notes
Eligible mutations are listed in the Food and Drug Administration (FDA) Trikafta prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212273s004lbl.pdf

8.4. In making this recommendation, the Committee considered that:

8.4.1. The CF disease trajectory is generally set before the age of six and there is no biologic or evidence-based reason to commence treatment at six years.

8.4.2. These data provided the necessary evidence for the safety profile of ELZ/TEZ/IVA in children aged two to five years with CF, which was similar to that in older children.

8.4.3. The health benefits of ELX/TEZ/IVA are known, and there is moderate to high-quality evidence for the appropriateness of Lung Clearance Index ($LCI_{2.5}$) as a reasonable surrogate for clinical endpoints in this context.

8.5. The Committee considered that the Special Authority criteria for ivacaftor should be aligned with that of ELX/TEZ/IVA in terms of the sweat chloride criterion as an "or" option.

Discussion

Māori impact

8.6. The Committee discussed the impact of funding ELX/TEZ/IVA for the treatment of CF in children aged two to five years on Pharmac's Māori health areas of focus and Māori health outcomes. The Committee considered that most relevant considerations had been well detailed previously and it had no new comments to add.

Populations with high health needs

8.7. The Committee discussed the health needs of children aged two to five years with CF among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding ELX/TEZ/IVA for the treatment of CF in children aged two to five years in this context. The Committee considered that most relevant considerations for these groups had been well detailed previously and it had no new comments to add.

Background

8.8. The Committee noted that ELX/TEZ/IVA is a triple CF transmembrane conductance regulator (CTFR) modulator that has been funded for people with CF aged six and over subject to Special Authority criteria since 1 April 2023.

8.9. The Committee noted that both the Respiratory Advisory Committee and PTAC have provided clinical advice on several occasions regarding the proposals to fund ELX/TEZ/IVA for Cystic fibrosis in children aged 12 years and older with F508del mutation(s) in the CFTR gene (see Application Tracker) and for Cystic fibrosis in children aged 6 years and older with F508del mutation(s) in the CFTR gene (see Application Tracker).

8.10. In April 2022, the Respiratory Advisory Committee noted that:

- Lung function progressively declines for patients with CF, even without pulmonary exacerbations.
- After an exacerbation, lung function does not usually return to the pre-exacerbation level.

8.11. In May 2022, PTAC:

- Considered the high health need of CF patients.
- Considered it unlikely there would be any *in vivo* evidence (due to low numbers) and that the *in vitro* model is well validated and accepted globally.
- Noted that younger patients who have percent predicted forced expiratory volume in one second (ppFEV1) lung function results perceived clinically as being within normal range may still have clinically significant lung disease and airway disruption.
- Considered that there is no biological reason to assume that younger patients with CF would respond differently to ELX/TEZ/IVA.

Health need

8.12. The Committee considered that CF is a heterogenous, progressive disease with pathophysiology beginning soon after birth and a subsequent disease trajectory established before six years of age. The Committee considered that the treatment approach with ELX/TEZ/IVA in CF is a lifelong preventative treatment and that there is no biologic reason to commence at six years of age.

8.13. The Committee was made aware of evidence from a prospective randomised controlled trial investigating therapies for exacerbations in 170 children with CF aged

up to five years in New Zealand and Australia (Byrnes et al. Thorax. 2013;68:643-51). The Committee considered that this reflects the current care of children with CF in New Zealand and exacerbation management. The Committee noted that there were 2,080 exacerbations overall, equivalent to 3.66 exacerbations per child per year with a median duration of 22 days and increasing with each year of age. The Committee noted that 413 of these exacerbations required hospitalisation with a median exacerbation duration of 50 days. The authors also reported data for exacerbations over time and outcomes at five years, with the effects of early disease (total exacerbations, exacerbations in the first two years, hospital exacerbations) being associated with bronchiectasis, FEV_1 and weight. The Committee considered that this provides evidence of the poor trajectory for children with CF being set early in life.

8.14. The Committee considered that parents of young children with CF may have significant anxiety around exacerbations and preserving lung function until children reach six years of age, potentially impacting health resource utilisation and parental behaviour (eg. willingness to send children to places of possible exposure to readily transmissible viral respiratory tract infections such as daycare).

8.15. The Committee was made aware of a case study in the USA in which a baby was born to a mother with CF and needed to start treatment from birth, otherwise they would have experienced ELX/TEZ/IVA withdrawal and acute pancreatitis. The Committee considered it possible that such a case could occur in New Zealand in future and that this could lead to an Exceptional Circumstances application to Pharmac.

Health benefit

8.16. The Committee noted that ELX/TEZ/IVA has been recommended for funding for children with CF aged two years and over with at least one F508del mutation (and in some cases, also for mutations responsive to ELX/TEZ/IVA based on *in vitro* data) by the Australian PBAC, Canadian CADTH, Scottish SMC and NICE in England/Wales.

8.17. The Committee noted that FEV_1 has been used as a surrogate endpoint in clinical trials of CF treatments for older children and adults, although it cannot reliably measure lung function in children younger than six years of age given that learning to undergo spirometry is very challenging for most in this age group. The Committee considered that a consequence of this is the otherwise-arbitrary staggering of age groups seen in the clinical trials undertaken for ELX/TEZ/IVA.

8.18. The Committee noted that $LCI_{2.5}$ is used as a surrogate in CF clinical trials in young children where FEV_1 is not feasible. The Committee noted that $LCI_{2.5}$ is the number of lung turnovers required to clear the lungs of a tracer gas to 1/40th (2.5%) the original concentration, and that higher $LCI_{2.5}$ indicates more ventilation inhomogeneity. The Committee noted that $LCI_{2.5}$ is unitless and is normalised for lung size (doesn't require adjustment for height or using z-scores). The Committee noted the following studies which generally used the same inert gas and equipment to investigate use of $LCI_{2.5}$ in CF:

8.18.1. A systematic review of $LCI_{2.5}$ for use in CF clinical trials for the European CF Society Clinical Trials Network (Kent et al. J Cyst Fibros. 2014;13:123-38). The authors report that $LCI_{2.5}$ is reliable and valid at detecting early airway dysfunction in the early 'silent' years where FEV_1 may be normal (n=23 studies), and that abnormal $LCI_{2.5}$ have a moderate/strong correlation with structural abnormalities (n = 21 studies). The authors concluded that $LCI_{2.5}$ is particularly indicated for multicentre trials in young children with CF and patients with early or mild CF-associated lung disease.

8.18.2. A study investigating lung function and magnetic resonance imaging (MRI) outcomes in 79 clinically stable children aged three to eight years with CF and 75 age-matched healthy controls (Frauchiger et al. J Cyst Fibros. 2024:S1569-1993(24)00074-2). The Committee noted there was a correlation between $LCI_{2.5}$ and ventilation, perfusion and morphology score. The Committee considered that, while uncertain, this appeared to also be predictive of clinical endpoints in some people.

8.18.3. A study of 34 people with CF aged six to 26 years of age with normal FEV_1, of which there was abnormal $LCI_{2.5}$ in 76.5% (Ellemunter et al. Respir Med. 2010;104:1834-42). The Committee considered that $LCI_{2.5}$ correlated well with computed tomography (CT) scan findings.

8.18.4. A retrospective cohort of 237 patients aged five years and older with CF in which $LCI_{2.5}$ performed similar to FEV_1 in predicting death and lung transplant in CF (Kurz et al. Eur Respir J. 2022;59:2100432).

8.18.5. A cohort study of 110 people with CF (including 43 children) and 61 controls reported greater sensitivity and specificity with $LCI_{2.5}$ compared with FEV_1 to discriminate those with CF. The authors reported that $LCI_{2.5}$ was correlated with quality of life as measured by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (O'Neill et al. Chest. 2016;150:1323-32).

8.18.6. A cohort study of 57 patients aged five to 18 years with CF and normal FEV_1 who were followed for one year. The authors report that $LCI_{2.5}$ was sensitive for predicting FEV_1 decline (Özsezen et al. Turk J Pediatr. 2024;66:297-308).

8.18.7. A cohort study of 63 patients aged five to 19 years with normal FEV_1 who were followed for one year (Vermeulen et al. Thorax. 2014;69:39-45). The authors reported that baseline $LCI_{2.5}$ predicted exacerbations and correlated with QOL (CFQ-R), even in the subgroup with normal FEV_1.

8.18.8. Evidence of a comparison between FEV_1 and $LCI_{2.5}$ in 48 preschool children with CF and 45 healthy controls aged three to five years (Aurora et al. Am J Respir Crit Care Med. 2011;183:752-8). The Committee noted that this small study was conducted in the population of interest, and that participants were taught spirometry which requires a considerable amount of effort. The authors reported changes in $LCI_{2.5}$ were seen before changes in FEV_1 in 35/48 (73%) of preschool children with CF while only 5/48 (10%) had abnormal FEV_1, and of those with abnormal $LCI_{2.5}$ at preschool age, 33/35 (94%) had an abnormal $LCI_{2.5}$ and 15/35 (43%) an abnormal FEV_1 by early school age. Only one child with abnormal FEV_1 at school age had had a normal preschool $LCI_{2.5}$. The Committee noted the limitations of the study but considered it suggested $LCI_{2.5}$ was a reasonable surrogate in most cases.

8.19. The Committee considered there was moderate to high-quality evidence for the appropriateness of $LCI_{2.5}$ as a reasonable surrogate for clinical endpoints in this context, noting that it is most often mapped to FEV_1 for ease and for regulatory reasons.

8.20. The Committee noted evidence from study 111: a phase III open-label study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of ELX/TEZ/IVA in 75 children with CF aged two to five years (Goralski et al. Am J Respir Crit Care Med. 2023;208:59-67). The Committee noted that Part B was conducted in the USA, Europe, and Australia and that the treatment period was 24 weeks. The Committee noted that 52/75 participants had F508del/minimal function genotypes and 23/75 had F508del/F508del genotype. The Committee considered this evidence was generalisable and highly relevant to the New Zealand context, noting the study population and CF management were very similar to that in New Zealand.

8.20.1. The Committee noted that the primary endpoints of study 111 were safety and tolerability. The Committee noted that:

- Most adverse events (AEs) were mild and expected for young children with CF.
- Some experienced exacerbations.
- There were some expected liver function abnormalities reported.
- There was a rare signal (1-2%) of behavioural change possibly occurring in those with a history of sleep or behavioural issues.
- There were serious AEs in two children (2.7%) which were behavioural change, leading to and resolving after discontinuation, and pulmonary exacerbation.

8.20.2. The Committee noted the change in secondary endpoints sweat chloride and $LCI_{2.5}$ occurred quickly and then plateaued with ongoing treatment.

8.21. The Committee noted data from presentation slides reporting an analysis of the 48-week extension (study 112), which showed that the plateaued sweat chloride and $LCI_{2.5}$ results remained as such over this longer term. The Committee noted there were two further treatment discontinuations: one due to liver function test increases and another due to behavioural changes. The Committee noted the data reported the rate of exacerbations increased from the rate reported in study 111 and considered the extent of this increase was expected with the ageing population despite longer term use of ELX/TEZ/IVA.

8.22. The Committee noted the following evidence around the surrogate outcomes $LCI_{2.5}$ and sweat chloride, and observational evidence for lumacaftor and ivacaftor in two- to five-year-olds:

- Urquhart et al. Pediatr Pulmonol. 2024;59:1449-53
- De Boeck et al Eur Respir J. 2013;41:203-16
- Barry et al. Thorax. 2014;69:586-7
- Bene et al. Clin Chim Acta. 2020:508:277-86
- Kim et al. J Cyst Fibros. 2024;23:436-42

8.23. The Committee also noted other data submitted by Vertex in its application (not cited above).

8.24. The Committee considered that safety was the most important outcome in this younger population given the health benefits of ELX/TEZ/IVA are known and based on good evidence in the older age groups. The Committee considered this data provided the necessary evidence for its safety profile in two- to five-year-olds, which was similar to that in older children with about 1-2% overall expected to discontinue the treatment.

8.25. The Committee considered that the key clinical outcome was improvement in lung function, measured as reduction in $LCI_{2.5}$. The Committee considered that there was evidence of a reduction in sweat chloride and meaningful changes in $LCI_{2.5}$ (correlating with FEV_1, high-resolution chest CT changes, and CFQ-R) which were consistent with the treatment effects in the studies of ELX/TEZ/IVA in six- to 11-year-olds with CF. The Committee considered that interpretation of the evidence for exacerbations was challenging due to the variable definitions used, but that it appeared to be decreased in this group compared with participants of the

Australasian CF Bronchoalveolar Lavage (ACFBAL) study (Australian Clinical Trials Registry: ACTRN0126050006656639).

8.26. The Committee considered it reasonable to assume that, for children with mutations not covered by study 111, the two- to five-year-old population would receive the same clinical benefit as six- to 11-year-olds. The Committee considered that while there is some uncertainty around this, there is no biologic or evidence-based reason to treat the two- to five-year-old group differently to those with rare genetic mutations with *in vitro* activity against ELX/TEZ/IVA aged six years or over.

8.27. The Committee noted the inherent challenges in producing clinical trial evidence for very young children and considered that future clinical trials investigating ELX/TEZ/IVA compared with ivacaftor in this younger age group would be highly unlikely to be undertaken (due to a lack of clinical equipoise and current funding for ELX/TEZ/IVA for this group in most jurisdictions).

Suitability

8.28. The Committee considered the ELX/TEZ/IVA granules likely to be well accepted and had no specific concerns about their suitability.

Cost and savings

8.29. The Committee considered that children with CF aged two to five years who have a gating mutation (with or without a F508del mutation) would be able to benefit from either ivacaftor or ELX/TEZ/IVA, and that if ELX/TEZ/IVA were funded approximately 80% of those would be expected to switch to ELX/TEZ/IVA. The Committee considered that the 20% remaining on ivacaftor would likely decrease over about five years to 5% remaining on it. The Committee considered that if ELX/TEZ/IVA were funded for this younger population, ivacaftor would need to remain available for this small proportion of patients who do not have mutations demonstrated to be ELX/TEZ/IVA-responsive and for those who could not tolerate ELX/TEZ/IVA. Members considered that this need related to individual/carer concerns about side effects of treatment with the ELX/TEZ components of Trikafta (whether potential or experienced) and the fact that some ivacaftor-responsive mutations may not yet have *in vitro* data demonstrating benefit with Trikafta.

8.30. The Committee considered that commencing treatment with ELX/TEZ/IVA at two years would incur a greater impact to the Combined Pharmaceutical Budget (CPB) over the disease lifetime, however, it would be expected to reduce the need for management of respiratory exacerbations, maintenance therapies including physiotherapy, and treatments for pancreatic insufficiency and inadequate growth (nutritional supplementation). The Committee considered that in future years where there is greater experience managing young children on ELX/TEZ/IVA, specialist engagement might also be reduced.

8.31. The Committee considered that there was little data to inform whether the initial (acute) proportional increase in ppFEV1 from baseline just after treatment initiation would be the same for children aged two to five years as it is for those aged six to 11 years. The Committee noted that baseline sweat chloride values reported in study 105 (Polineni et al. Presented at 46th European CF Conference, June 2023) were similar to those in study 111, and baseline $LCI_{2.5}$ values were different, which members considered was likely due to the reduced damage in the younger patients treated with ELX/TEZ/IVA.

8.32. The Committee considered that commencing ELX/TEZ/IVA in children aged two to five years would be the best strategy to prevent deterioration, preserve normal lung function and prevent any meaningful decline. However, the Committee considered it

would not entirely prevent any decline in lung function before the age of six, as damage can occur within the first two years of life and lung function decline can occur secondary to non-CF causes. The Committee considered that in the absence of long-term data, it was reasonable to assume that ELX/TEZ/IVA may lead to avoidance of accelerated long-term ppFEV1 decline in a very high (~95%) proportion of people.

8.33. The Committee considered that uptake of ELX/TEZ/IVA in children aged two to five years might be about 80%, as approximately 20% of parents might prefer for their otherwise well children to not commence lifelong treatment until they become symptomatic.

Funding criteria

8.34. The Committee considered that there are no specific clinical features or investigative results that could indicate a need to start ELX/TEZ/IVA, given its role as a preventative medicine to be commenced prior to deterioration. The Committee therefore considered that simply changing the age-based criterion in the Special Authority was appropriate.

8.35. The Committee considered it preferable to retain the sweat chloride criterion as an "or" option in the Special Authority criteria and noted that this is usually performed during a diagnosis of CF prior to genetic testing. The Committee noted that some genetic mutations will not be known or detected in New Zealand and thus limiting eligibility to known and detectable mutations may disadvantage some individuals who would meet criteria with one F508del mutation and a sufficient sweat chloride value.

8.36. The Committee considered that the Special Authority criteria for ivacaftor should be aligned with that of ELX/TEZ/IVA in terms of the sweat chloride criterion as an "or" option.

Summary for assessment

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

<table>
<tr><td rowspan="2">Population</td><td>Group 1: Children with CF aged 2-5 years with at least one F508del mutation in the CFTR gene: F/F, F/MF, F/RF, F/other.

Gating mutations (F/G) presented in separate sub-population.

(~82% of children with CF)</td><td>Group 2: Children with CF aged 2-5 years who have rare mutations responsive in vitro to ELX/TEZ/IVA (non-F/rare)

Gating mutations (non-F/G) presented in separate sub-population.

(~2% of children with CF)</td><td>Group 3: Children with CF aged 2-5 years who have a gating mutation (with or without a F508del mutation) with funded access to ivacaftor.

(16% of children with CF, evenly split between F/G and non-F/G mutations)</td></tr>
<tr><td colspan="3">Safety and efficacy of ELX/TEZ/IVA in children aged less than 2 years have not been established (trials ongoing).</td></tr>
<tr><td>Intervention</td><td colspan="3">Trikafta (ivacaftor–tezacaftor–elexacaftor plus ivacaftor; ELX/TEZ/IVA) plus best supportive care~

- Daily dose provided in two sachets taken 12 hours apart (morning and evening)</td></tr>
</table>

<table>
<tr><td></td><td colspan="3">- Dose based on age and weight, with two fixed-dose combinations available for children aged under 6:
o weight <14kg: elexacaftor 80mg/ tezacaftor 40mg/ ivacaftor 60mg plus ivacaftor 59.5 mg
o weight ≥ 14kg: elexacaftor 100mg/ tezacaftor 50mg/ ivacaftor 75mg plus ivacaftor 75 mg

ELX/TEZ/IVA will be co-administered with best supportive care~

Continue treatment until clinical decision made to reduce dose or stop treatment with ELX/TEZ/IVA (e.g. due to liver complications).</td></tr>
<tr><td rowspan="2">Comparator(s)</td><td>Age 2-5 years:
Best supportive care~</td><td>Age 2-5 years:
Best supportive care~</td><td>Age 2-5 years:
Ivacaftor plus best supportive care</td></tr>
<tr><td colspan="3">Age 6 years and older: ELX/TEZ/IVA plus best supportive care~</td></tr>
<tr><td>Outcome(s)</td><td colspan="3">The key therapeutic intent of ELX/TEZ/IVA is to improve overall survival and quality of life by stopping disease progression.
Key outcome measures:
• improvement and/or reduced deterioration in lung function
• adverse effects of treatment
Other relevant outcome measures include:
• reduced pulmonary exacerbations
• reductions in sweat chloride concentration
• reduced need for hospitalisation and other treatments (e.g. antibiotics, lung transplants, chest physiotherapy)
• weight-for-age z-score
• improved health-related quality of life
• improved overall survival</td></tr>
<tr><td colspan="4">Key:
~ Best supportive care includes treatments that manage the symptoms and complications of CF: mucolytics, osmotic agents, antibiotics, bronchodilators, enzyme and vitamin replacements and supplements, and chest physiotherapy (Respiratory Advisory Committee, August 2021)

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.</td></tr>
</table>

9. Azelastine hydrochloride + fluticasone propionate nasal spray for allergic rhinitis

Application

9.1. The Committee reviewed the clinician application for azelastine hydrochloride + fluticasone propionate nasal spray for allergic rhinitis.

9.2. The Committee also reviewed evidence for azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of adenoid hypertrophy.

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

Recommendation

9.4. The Committee **recommended** that azelastine hydrochloride + fluticasone propionate nasal spray be listed with a **medium priority** for the treatment of rhinitis/rhinoconjunctivitis, within the context of treatment of respiratory disease, subject to the following Special Authority criteria:

> **Initial application** – (rhinitis and/or rhinoconjunctivitis) from any relevant practitioner. Approvals valid without further renewal for applications meeting the following criteria:
> Both:

1. Patient has rhinitis and/or rhinoconjunctivitis; and
2. Patient has had an adequate trial of oral antihistamines and intranasal corticosteroids and has experienced insufficient control of symptoms.

9.5. In making this recommendation, the Committee considered that:

9.5.1. There are limited funded pharmaceutical treatment options available for people with rhinitis symptoms affecting their quality of life, who are not receiving adequate treatment benefit from intranasal corticosteroids (ICS) and oral antihistamines.

9.5.2. Azelastine hydrochloride + fluticasone propionate nasal spray provides slightly better outcomes than either individual component on its own.

9.5.3. Nasal sprays can be challenging to administer, and this can lead to wasted product dependent on individual technique.

9.5.4. There is the potential for more than 100,000 people to be eligible for the treatment if it were to be funded.

9.6. The Committee **recommended** that azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of adenoid hypertrophy be **declined**.

9.7. In making this recommendation, the Committee considered that the evidence for the health benefit of azelastine hydrochloride + fluticasone propionate nasal spray for adenoid hypertrophy is weak, being based on single arm trials conducted over a short period of time which reported on surrogate outcomes but not clinical benefits.

Discussion

Māori impact

9.8. The Committee discussed the impact of funding azelastine hydrochloride + fluticasone for the treatment of rhinitis/rhinoconjunctivitis on Māori health outcomes. The Committee noted that Respiratory Health | Romaha Ora is one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus.

9.9. The Committee noted the International Study of Asthma and Allergies in Childhood (ISAAC) survey reported that Māori children and adolescents experience symptoms of rhinoconjuntivitis including severe rhinoconjunctivitis more frequently than NZ European children (Moyes et al. J Paediatr Child Health. 2012;48:913-20)

Populations with high health needs

9.10. The Committee discussed the health needs of people with rhinitis and rhinoconjunctivitis among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding azelastine hydrochloride + fluticasone in this context.

9.10.1. The Committee noted the ISAAC study reported that Pacific children and adolescents experience symptoms of rhinoconjunctivitis including severe rhinoconjunctivitis more frequently than NZ European children and adolescents (Moyes et al. 2012).

9.10.2. The Committee did not identify any other group with known inequitable health outcomes associated with rhinitis, but noted that the lack of available evidence did not exclude the possible presence of such inequities.

Background

9.11. The Committee noted that Pharmac had not previously received advice on pharmaceutical treatments for rhinitis and rhinoconjunctivitis. The Committee noted Pharmac has funded oral loratadine and beclomethasone dipropionate nasal spray since 1994, oral cetirizine and promethazine since 1995 and fluticasone propionate nasal spray since 2010. The Committee noted that, as a part of its annual tender process, Pharmac will fully fund fexofenadine tablets from February 2025.

9.12. The Committee noted that pharmaceutical treatments for adenoid hypertrophy have not previously been considered by Pharmac.

9.13. The Committee noted that people with vasomotor rhinitis would be eligible for azelastine hydrochloride + fluticasone propionate treatment based on the proposed criteria for rhinitis and/or rhinoconjunctivitis and noted that it can be difficult to distinguish between vasomotor rhinitis/ rhinoconjunctivitis and other types of rhinitis and rhinoconjunctivitis (including allergic forms). The Committee noted that vasomotor rhinitis is very difficult to treat and that anti-cholinergic agents are the preferred treatment choice, although currently there is a lack of their availability globally.

Health need

9.14. The Committee noted that in February 2017, PTAC noted that seasonal allergic rhinitis (hayfever) is very common in New Zealand, affecting up to 30% of adults and 40% of children. The Committee noted that allergic rhinitis is characterised by symptoms such as sneezing, nasal pruritus, airflow obstruction, and (mostly) clear nasal discharge. This is caused by IgE mediated reactions against inhaled allergens. Often symptoms are accompanied by allergic conjunctivitis with itchy, red, watery, and/or swollen eyes. The Committee considered that allergic rhinitis can cause impairment of cognition and decreased daytime performance in work and educational settings, and people can experience negative impacts on their daily activities when they have more severe symptoms.

9.15. The Committee noted the Allergic Rhinitis and its Impact on Asthma (ARIA) survey estimated 88% of allergic rhinitis to be moderate to severe (Small et al. CTA. 2013:3;33).

9.16. The Committee noted that allergic rhinitis is notably present in about 75% to 80% of all people with asthma and in nearly 100% of people with allergic asthma. The Committee noted that allergic rhinitis is associated with increased asthma-related hospitalisations and higher total annual medical costs (Dykewicz et al. J Allergy Clin Immunol. 2020; 146: 721-67).

9.17. The Committee noted applicant-provided treatment paradigms from the American Rhinology Society and the American Academy of Otolaryngic Allergy, and noted the applicants proposal that azelastine + fluticasone nasal spray be added as a treatment option for people who have experienced insufficient control of symptoms from ICS treatments or oral antihistamines.

9.18. The Committee considered that there are limited funded pharmaceutical treatment options available for people with rhinitis symptoms, especially for those where symptoms are affecting their quality of life and among those who are not receiving adequate treatment benefit from ICS and oral antihistamines.

9.19. The Committee noted the International Study of Asthma and Allergies in Childhood (ISAAC) survey reported that Māori children and adolescents experience symptoms of rhinoconjuntivitis including severe rhinoconjunctivitis more frequently than NZ European children and adolescents (six to seven year old prevalences of: 12.1% versus 11.3%; 13- to 14- year old prevalences of: 21.5% versus 16.7%, for Māori

versus European ethnicity, respectively) (Moyes et al. J Paediatr Child Health. 2012;48:913-20).

9.20. The Committee noted the ISAAC study reported that Pacific children and adolescents experience symptoms of rhinoconjunctivitis including severe rhinoconjunctivitis more frequently than European/Pakeha children and adolescents (six- to seven-year-old prevalences of: 11.6% versus 11.3%; 13-to-14-year prevalence: 21.5% versus 16.7%, for Pacific versus European children or adolescents, respectively).

9.21. The Committee noted that adenoid hypertrophy is a prevalent childhood disease that presents symptoms related to airway blockage such as snoring, apnoeic episodes, nasal speech, and mouth breathing (Biligili et al. Ear Nose Throat J. 2023; 102: 28-34). The Committee noted that it is estimated that 80% of children with adenoid hypertrophy experience eustachian tube dysfunction (Manno et al. Ear Nose Throat J. 2021).

Health benefit

9.22. The Committee noted azelastine hydrochloride is an antihistamine with histamine-1 receptor antagonist activity and fluticasone propionate is a glucocorticoid with anti-inflammatory activity.

9.23. The Committee noted azelastine hydrochloride + fluticasone propionate nasal spray is approved by Medsafe for the symptomatic treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis in adults and children 12 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is appropriate. The Committee noted the treatment is not currently approved by Medsafe for adenoid hypertrophy or for children under the age of 12 years.

9.24. The Committee noted results from a meta-analysis of three multicentre, randomised, double-blind, placebo and active controlled, parallel group trials assessing the efficacy of azelastine hydrochloride + fluticasone propionate nasal spray (AZ/FP) in comparison to azelastine hydrochloride alone (AZ) , fluticasone alone (FP), and placebo (N = 3398) (Carr et al. JACI. 2012:129;1282-9). Members noted that the trial populations had moderate to severe allergic rhinitis but had not necessarily been chosen based on receiving poor response from ICS and antihistamines. The Committee noted that AZ/FP reduced the mean reflective total nasal symptom score from baseline (-5.7 [SD, 5.3]) more than FP (-5.1 [SD, 4.9], $P<0.001$), AZ (-4.4 [SD, 4.8], $P<0.001$), and more than placebo (-3.0 [SD, 4.2], $P<0.001$). The Committee noted the total nasal symptom score (TNSS) is defined as the sum of four nasal symptom scores: rhinorrhoea, nasal congestion, nasal itching, and sneezing. The Committee considered the results showed AZ/FP provided slightly better outcomes than AZ or FP alone.

9.25. The Committee also noted results from the following publications regarding the efficacy and safety of azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of allergic rhinitis and rhinoconjunctivitis:

- Meltzer et al. Allergy Asthma Proc. 2012;33: 324-32
- Ratner et al. Ann Allergy Asthma Immunol. 2008; 100:74-81
- Hampel et al. Ann Allergy Asthma Immunol. 2010; 105: 168-73
- Debbaneh et al. Otolaryngol Head Neck Surg. 2019; 161: 412-8.

9.26. The Committee considered the results from the discussed evidence supported the results reported in the Carr et al. 2012 meta-analysis – that the azelastine hydrochloride + fluticasone propionate nasal spray provides slightly better outcomes than either of the individual components on their own, but that this difference is

marginal, and may not be clinically significant for many people. However, the Committee considered the rapid onset of action of the combination product may improve patient acceptance and adherence to treatment. The Committee considered that azelastine hydrochloride + fluticasone propionate nasal spray is not associated with any clinically significant risks in comparison to currently funded treatments.

9.27. The Committee considered the following evidence regarding the efficacy and safety of azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of adenoid hypertrophy:

- Biligili et al. Ear Nose Throat J. 2023;102:28-34
- Bilgili et al. Ear Nose Throat J. 2023; 102: 198-203

9.28. The Committee noted the above studies were single arm trials that were conducted over a short period of time. The Committee noted the trials reported on surrogate outcomes, but not on clinical benefits, and considered the surrogate outcomes to be subjective. The Committee considered the evidence supporting the use of azelastine hydrochloride + fluticasone propionate nasal spray for the treatment of adenoid hypertrophy was weak.

Suitability

9.29. The Committee considered that like other funded nasal sprays, azelastine hydrochloride + fluticasone propionate nasal spray can be challenging to administer, and this could lead to wasted product.

Cost and savings

9.30. Members noted that, given the estimation approximately 30% of New Zealanders have some degree of allergic rhinitis and many of those people would meet the proposed criteria for azelastine hydrochloride + fluticasone propionate nasal spray, there is the potential for more than 100,000 people to be eligible for the treatment if it were to be funded.

9.31. Members noted that azelastine hydrochloride + fluticasone nasal spray would be anticipated to replace a proportion of use of fluticasone propionate or budesonide nasal sprays, and oral antihistamine use.

Summary for assessment

9.32. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for azelastine hydrochloride + fluticasone propionate nasal spray if it were to be funded in New Zealand for rhinitis/rhinoconjunctivitis. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People aged ≥12 with rhinitis and/or rhinoconjunctivitis who have insufficient control of symptoms following an adequate trial of oral antihistamines and intranasal corticosteroids.
Intervention	One spray (137 mcg of azelastine hydrochloride with 50 mcg of fluticasone propionate) of AZ/FP nasal spray into each nostril twice daily (morning and evening).

Comparator(s) (NZ context)	Inhaled corticosteroid (fluticasone propionate 50 µg per nostril twice daily or budesonide 100 mcg per nostril per day) with or without daily oral antihistamines.
Outcome(s)	Improvement in reflective total nasal symptom score (rTNSS) compared to comparator. Over a 14-day treatment period, azelastine hydrochloride with fluticasone propionate nasal spray (MP29-02) administration reduced the mean rTNSS from baseline (-5.7 ± 5.3), significantly more than fluticasone propionate (-5.1 ± 4.9) (Carr et al. JACI. 2012:129;1282-9).
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

10. Rituximab for the treatment of systemic sclerosis interstitial lung disease

Application

10.1. The Committee reviewed the application for rituximab for the treatment of interstitial lung disease (ILD) due to systemic sclerosis (SSc) in individuals whose disease is not responsive to, or intolerant to, mycophenolate mofetil.

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

Recommendation

10.3. The Committee **recommended** that rituximab for the treatment of systemic sclerosis interstitial lung disease in people whose disease is not responsive or intolerant to mycophenolate mofetil be funded with a **high priority,** in the context of respiratory disease, subject to the following Special Authority criteria:

> **Initial application – (Interstitial lung disease associated with systemic sclerosis)** from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. Patient has interstitial lung disease associated with systemic sclerosis confirmed by high resolution computed tomography; and
> 2. Any of the following:
> 2.1. Patient has trialled for at least 3 months; and not received adequate benefit from, mycophenolate mofetil; or
> 2.2. Patient has experienced intolerable side effects from mycophenolate mofetil; or
> 2.3. Patient is contraindicated to mycophenolate mofetil.

10.4. The Committee **recommended** that rituximab for the second-line treatment of connective tissue disease related interstitial lung disease be funded with a **high priority,** in the context of respiratory disease, subject to the following Special Authority criteria:

> **Initial application – (Interstitial lung disease associated with connective tissue disease)** from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Both:

1. Patient has interstitial lung disease associated with connective tissue disease confirmed by high resolution computed tomography; and
2. Any of the following:
    2.1. Patient has trialled and not received adequate benefit from a disease modifying anti-rheumatic drug for at least 3 months; or
    2.2. Patient has experienced intolerable side effects from a disease modifying anti-rheumatic drug; or
    2.3. Patient is contraindicated to all appropriate first line disease modifying anti-rheumatic drugs.

10.5. In making these recommendations, the Committee considered:

10.5.1. The high unmet health need of people with ILD

10.5.2. That rituximab offers a similar health benefit to cyclophosphamide with a less toxic side effect profile.

10.5.3. That rituximab has the potential to delay or prevent the use of cyclophosphamide in this context.

10.5.4. The similar health need of individuals who have connective tissue disorder related interstitial lung disease.

10.5.5. Further deliberation is necessary to finalise the Special Authority criteria.

10.6. The Committee recommended that the Rheumatology Advisory Committee review this meeting record and the proposed Special Authority criteria.

Discussion

Māori impact

10.7. The Committee discussed the impact of funding rituximab for the treatment of SSc ILD on Māori health areas of focus and Māori health outcomes. The Committee noted a study at Middlemore Hospital reported one person out of 74 with SSc was Māori (Ng et al. N Z Med J. 2007;120:U2537). The Committee considered that this much lower reported rate than expected demographically might represent a barrier to healthcare with under-identification of cases in Māori rather than a true low prevalence. The Committee concluded there is a lack of evidence on the true prevalence of ILD due to SSc in Māori.

Populations with high health needs

10.8. The Committee discussed the health needs of people with SSc ILD among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding rituximab in this context.

10.8.1. The Committee noted the above study at Middlemore Hospital reported three people out of 74 with SSc were Pacific peoples. As with Māori (above), the Committee considered that this might be an under-count and represent a barrier to healthcare.

10.8.2. The Committee considered that access to treatment would require access to specialists, and a variety of scans, which can be more challenging for people in rural communities to access, representing a barrier to treatment access.

10.8.3. The Committee further considered that individuals may need to self-advocate, which can require accessing healthcare resources that do not the needs of some populations (Milette et al. Disabil Rehabil. 2019;41:2506-15). The Committee considered this also represented a barrier to accessing treatment for ILD.

Background

10.9. The Committee noted rituximab is funded for a range of indications.

Health need

10.10. The Committee previously noted in April 2022 that ILD describes a heterogenous group of disorders characterised by progressive inflammation and fibrosis of the lung tissue. The Committee noted that a subset of people with ILD experience a decline in lung function with progressive symptoms accompanied by a reduced quality of life and can be described as having progressive fibrosing ILD (PFILD), however, there is no universally accepted definition.

10.11. The Committee noted systemic sclerosis (SSc), also known as scleroderma, is a rare immune-mediated disease characterised by inflammatory, autoimmune, fibrotic, and vascular pathology affecting multiple organ systems including the skin, lungs, heart, gastrointestinal tract, and kidneys. Lung involvement, manifesting as ILD or pulmonary hypertension, is the most common cause of premature mortality in people with SSc (Pope et al. Nature Reviews Rheumatology. 2023;19:212-26).

10.12. The Committee noted that SSc is heterogeneous in terms of organ involvement, disease progression and outcome. The Committee noted those with limited cutaneous SSc (CREST syndrome) experience symptoms on the hands but more limited ILD symptoms, and this form of SSc is associated with pulmonary arterial hypertension. The Committee noted more diffuse cutaneous SSc presents more frequently with ILD. The Committee noted another variant, systemic sclerosis sine scleroderma, shares many visceral, serological, and vascular manifestations but does not present with skin thickening. The Committee noted that SSc can also overlap with other connective tissue diseases (CTD).

10.13. The Committee noted the prevalence of SSc is estimated at 30 to 120 cases per million (Pope et al. 2023). Based on this prevalence, in New Zealand it is estimated that 400 people have SSc. The applicant estimated that 30% of people with SSc would have associated ILD. Of this population, 50% would receive mycophenolate and half of them would not experience a response or are contraindicated to mycophenolate mofetil. The applicant considered that the population who would be eligible for funding of rituximab as proposed would be 30 people.

10.14. The Committee noted ILD is a significant cause of morbidity and mortality in people with SSc and is the leading cause of SSc-related death in people with SSc, contributing to 35% of deaths. Additionally, people with SSc may have other manifestations of SSc, including pulmonary hypertension, oesophageal dysmotility, and gastroesophageal reflux disease, which may affect outcomes for people with ILD associated with SSc (SSc-ILD) (Raghu et al. Am J Respir Crit Care Med. 2023;209:137-52).

10.15. The Committee noted that early ILD is frequently asymptomatic. The most common symptoms of SSc-ILD are fatigue, breathlessness (initially on exertion), and dry cough. Chest pain is infrequent, and haemoptysis is rare. The most characteristic finding of ILD on physical examination is bibasilar fine inspiratory crackles (ie "Velcro" rales) at the lung bases. Signs of pulmonary heart disease (cor pulmonale) can be seen with advanced ILD, but are more commonly associated with pulmonary hypertension, which may occur in SSc as a separate process or in association with ILD (UpToDate. Clinical manifestations, evaluation, and diagnosis of interstitial lung disease in systemic sclerosis (scleroderma). Updated April 2023).

10.16. The Committee noted lower and declining forced vital capacity (FVC) and lower diffusing capacity for carbon monoxide (DLCO) were reported as predictive of mortality. Male gender, higher modified Rodnan skin score, and reflux or dysphagia

symptoms were the strongest predictors for FVC decline over five years. Males have also demonstrated higher rates of FVC decline and increased mortality in randomised trials (UpToDate. Treatment and prognosis of interstitial lung disease in systemic sclerosis (scleroderma). Updated Feb 2024).

10.17. The Committee noted that the majority of people with SSc ILD presented with nonspecific interstitial pneumonia (NSIP), whilst others can present with usual interstitial pneumonia (UIP). The Committee considered that people with SSc ILD may have comorbid conditions that can contribute to respiratory morbidity such as pulmonary arterial hypertension, congestive heart failure, drug toxicity, infection or aspiration.

10.18. The Committee noted that idiopathic inflammatory myopathies (IIM) are associated with ILD that can be rapidly progressive.

10.19. The Committee considered that SSc-ILD is often stable or very slowly progressing and is treated mainly with mycophenolate in the first line setting. The Committee considered a small population have rapidly developing disease. The Committee considered currently funded second line agents such as methotrexate were less effective, whilst cyclophosphamide was more toxic and inappropriate for people with mild stable ILD.

10.20. The Committee noted that key treatment outcomes are reduction in lung infiltrate, improvement in lung function and quality of life, as well as slowing or stopping disease progression.

10.21. The Committee considered that multidisciplinary meeting (MDM) discussions are used in clinical practice to decide on the best treatment pathways for individuals with these diseases.

10.22. The Committee considered a very small proportion of people with ILD would have severe progressive disease and require lung transplantation or palliative care.

Health benefit

10.23. The Committee considered rituximab would be used to reduce inflammation and prevent fibrosis in the lungs. The Committee noted that if antifibrotics were funded for progressive fibrotic ILD these would be used after rituximab to treat the progression of established fibrosis but not the inflammation.

10.24. The Committee noted the RECITAL trial (Maher et al. Lancet Respir Med 2023;11:45-54), which evaluated the effect of rituximab compared to cyclophosphamide in people with severe or progressive ILD related to CTD. SSc was the CTD type in 37-40% of participants.

10.24.1. The study reported the following mean rate of change in forced vital capacity at 48 weeks:

- cyclophosphamide: 138 mL (SD 440)
- rituximab: 112 mL (SD 249)
- adjusted difference: –58 mL (95% CI –178, 62; P=0.345)

10.24.2. The study also reported the mean change in EuroQol- 5-dimension (EQ-5D) score (a measure of quality of life) from baseline at week 48 was:

- cyclophosphamide: –1.2 (SD 23.5)
- rituximab: 3.9 (SD 15.8)
- adjusted difference: 4.77 (95% CI, –1.73, 11.27; P= 0.150)

10.24.3. The Committee noted that whilst the EQ-5D score favoured rituximab, this was not statistically significant. The 48-week adjusted difference in St George's respiratory questionnaire score (SGRQ), a measure of respiratory relevant quality of life, favoured cyclophosphamide but was also not statistically significant.

10.24.4. The Committee noted that people with IIM were the biggest cohort within the trial. The Committee noted the trial was a single small randomised controlled study, but considered it provided the best evidence of efficacy in people with IIM ILD. The Committee considered the proportion of people with each form of ILD recruited to the clinical trial would be representative of the clinical population in New Zealand.

10.24.5. The Committee considered rituximab had a similar clinical efficacy to cyclophosphamide, however had a less toxic side effect profile.

10.25. The Committee noted the following studies:

- Sircar et al. Rheumatology (Oxford). 2018; 57: 2106-13
- Daoussis et al. Semin Arthritis Rheum. 2017; 46: 625-31
- Yoshifuji et al. Mod Rheumatol. 2023;33: 1068-77
- Boonstra et al. RMD Open. 2017;3:e000384
- Daoussis et al. Rheumatology (Oxford). 2010;49:271–80
- Macrea et al. Ann Am Thorac Soc. 2024;21:317-27
- Birrurukwisitsak et al. Clin Rheumatol. 2021;40:2779-89
- Goswami et al. Rheumatology (Oxford). 2021;60:557-67
- Erre et al. J Clin Med. 2020;9:2560

10.25.1. The Committee considered that these studies were of lower quality, with a small number of participants included, and were less generalisable to the New Zealand population. The Committee considered overall these studies indicated that there was similar or slightly better health benefit from rituximab than cyclophosphamide.

10.25.2. The Committee considered overall the meta-analyses (reported by Macrea et al. 2024; Birrurukwisitsak et al. 2021; Goswami et al. 2021; Erre et al. 2020) were too small and heterogeneous to draw conclusions on efficacy.

10.26. The Committee considered there was less evidence for the use of rituximab in the treatment of CTD related ILD, however, that there may be benefit for this population.

10.27. The Committee considered overall the evidence was of weak strength, with just one randomised controlled study that was generalisable to the New Zealand population. However, the Committee considered the effects of rituximab were biologically plausible and that the health benefits seen in people with SSc ILD are similar to those in people with IIM ILD, and it was reasonable to assume similar health benefits would be observed in people with other CTD related ILDs.

10.28. The Committee noted the health benefit of rituximab in terms of forced vital capacity, respiratory related quality of life, and overall quality of life may last for between six months to a year.

10.29. The Committee considered individuals who receive rituximab may need to avoid live immunisations, undergo monitoring including for neutrophil and lymphocyte counts, and may experience severe or recurrent infections. However, the Committee considered that severe adverse effects with rituximab, including progressive

multifocal leukoencephalopathy, are very rare, as are the formation of anti-drug antibodies.

10.30. The Committee considered approximately 20-30% of rituximab recipients may experience a mild infusion reaction, whilst 3% may experience a severe reaction. The Committee considered >10% may experience adverse effects including weight gain, abdominal pain and pulmonary or liver toxicity. The Committee considered, however, that rituximab was associated with a less severe adverse event profile than cyclophosphamide.

Suitability

10.31. The Committee noted that while both cyclophosphamide and rituximab are intravenous infusions, rituximab is administered less frequently during initiation of treatment and therefore overall requires less time receiving infusions on average for the person being treated. The Committee considered this would reduce time spent away from whānau and paid employment.

Cost and savings

10.32. The Committee considered that rituximab is only appropriate for treating severe disease and would not be appropriate for mild or non-progressive disease.

10.33. The Committee considered it would be appropriate to consider safety or reduction in adverse events as an outcome.

10.34. The Committee considered rituximab would replace the use of cyclophosphamide, methotrexate or other disease modifying anti-rheumatic drugs or corticosteroids. The Committee considered it may be used in combination with anti-fibrotic medications if these were funded in the future for PFILD. The Committee considered that cyclophosphamide is an appropriate comparator for people with severe progressive disease, not for those who experience mild or non-progressive disease. The Committee noted that mesna is used in combination with cyclophosphamide.

10.35. The Committee considered between 50-70% of people with SSc have ILD, however many of these would have mild disease or not present clinically.

10.36. The Committee considered the majority (up to 95%) of people would receive 1 g rituximab on day zero and day 15, repeated six to 12 monthly. The Committee considered that a few people would receive a reduced 500 mg dose due to low body weight or adverse effects. The Committee considered anecdotal evidence that some individuals may need more frequent dosing (every four months) due to the return of disease symptoms.

10.37. The Committee considered estimates of 80% of people receiving mycophenolate to be too high but did note that such estimates depend on the definition of ILD. The Committee noted that people with mild disease or rheumatoid arthritis related ILD would not be receiving mycophenolate.

10.38. The Committee estimated that people with SSc ILD would on average visit a general practitioner six times per year and a specialist four to six times per year (two to three visits for rheumatology and two to three for respiratory). The Committee also considered a person with SSc ILD may have one CT scan per year, monthly blood tests, one to two pulmonary function tests a year, and chest x-rays infrequently.

10.39. The Committee estimated that a person with SSc ILD may be hospitalised once every five years, and have a medical day stay on four days per year with rituximab compared with seven for cyclophosphamide. The Committee considered that a day stay was defined as a visit to the hospital lasting more than three hours in duration.

Funding criteria

10.40. The Committee considered it would be appropriate to consider funding for all individuals with CTD related ILD. The Committee considered this would increase the treatment population size by two and a half times.

Summary for assessment

10.41. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for rituximab if it were to be funded in New Zealand for the treatment of CTD related ILD. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with severe connective tissue disease (CTD) associated interstitial lung disease (ILD) (CTD-ILD) who have not received benefit on prior treatments: • Systemic sclerosis (SSc)-ILD, idiopathic inflammatory myopathy (IIM)-ILD, mixed connective tissue disease (MCTD)-ILD prior treatment is mostly with mycophenolate. • Systemic lupus erythematosus (SLE)-ILD rarely reaches the severity to require these medications. • Rheumatoid arthritis (RA)-ILD includes first line agents methotrexate, leflunomide and tumour necrosis factor (TNF)-alpha inhibitors like etanercept and adalimumab. These are likely to also be used first line for RA-ILD rather than mycophenolate for the treatment of arthritis.
Intervention	Rituximab is dosed as either: 500 mg – 1000mg on day zero and day 15, repeated six to 12 monthly. 375 mg/m^2 body surface area (BSA) weekly for four weeks, repeated six to 12 monthly.
Comparator(s)	Cyclophosphamide 600 mg/m^2 every four weeks, for six months.
Outcome(s)	**Equivalent lung function outcomes** Forced vital capacity (FVC) improved from baseline in the cyclophosphamide group (unadjusted mean increase 99 mL [SD 329]) and the rituximab group (97 mL [234]); in the adjusted mixed-effects model, the difference in the primary endpoint at 24 weeks was –40 mL (95% CI –153 to 74; p=0·49) between the rituximab group and the cyclophosphamide group (Maher et al. Lancet Respir Med 2023; 11: 45–54). **Improvements in quality of life** Compared with baseline, EQ-5D was improved at week 24 in the cyclophosphamide group (3·5 points [20·5]) and in the rituximab group (6·2 points [17·0]); at week 48, the change was –1·2 points (23·5) in the cyclophosphamide group and 3·9 points (15·8) in the rituximab group (Maher et al. Lancet Respir Med 2023; 11: 45–54). The QOL benefits of rituximab are considered to be roughly equivalent to cyclophosphamide's. **Other outcomes** • Reduction in adverse events with rituximab compared to cyclophosphamide
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Dupilumab & mepolizumab - Chronic rhinosinusitis with nasal polyposis (CRSwNP), maintenance treatment of uncontrolled disease

Application

11.1. The Committee reviewed the supplier application from GlaxoSmithKline limited (GSK) for mepolizumab (Nucala) for the treatment of patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) who have received prior nasal polyp surgery and whose disease remains inadequately controlled with standard of care.

11.2. The Committee noted:

11.2.1. A consumer application for dupilumab (Dupixent) for the maintenance treatment of CRSwNP in adults whose disease is not controlled. The Committee noted that dupilumab had not been submitted to Medsafe at the time of the meeting.

11.2.2. Letters of support from New Zealand clinicians pertaining to mepolizumab and/or dupilumab for inadequately controlled CRSwNP.

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

Recommendation

11.4. The Committee **recommended** that mepolizumab be funded for the treatment of severe chronic rhinosinusitis with nasal polyps (CRSwNP) with a **high priority,** within the context of treatment of respiratory disease, subject to the following Special Authority criteria:

Initial application — Severe chronic rhinosinusitis with nasal polyps
Applications only from a respiratory physician, clinical immunologist, ear nose and throat specialist (ENT), or relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria.
All of the following:

1. Diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP); and
2. No other clear indication for surgery on medical imaging; and
3. Either:
    - 3.1. Both:
        - 3.1.1. Patient has had at least one comprehensive sinus operation (which includes frontal sinus drill-out) plus a course of oral corticosteroids for the treatment of nasal polyps (see Note 1); and
        - 3.1.2. Recurrence has occurred within one year of the most recent comprehensive surgery; or
    - 3.2. Patient is not a candidate for comprehensive sinus surgery due to comorbidities or contraindications to the surgery; and
4. Patient has severe CRSwNP defined as having at least two of the following:
    - 4.1. Bilateral endoscopic nasal polyp score of at least five (out of a maximum score of eight, with a minimum score of two in each nasal cavity); or
    - 4.2. Disease symptoms have a severe impact on individual's quality of life (eg due to loss of smell, nasal congestion, rhinorrhoea); or
    - 4.3. High symptom burden (score ≥40) on sinonasal outcome test (SNOT-22) questionnaire (see Note 2); and
5. Patient has a blood eosinophil count of ≥0.3 x 10^9 cells/L in the last 12 months; and
6. Disease inadequately controlled with optimised nasal polyps therapy (see Note 3).

Note 1: Comprehensive sinus operations include comprehensive functional endoscopic sinus surgery (FESS) with frontal sinus drill-out. Standard FESS alone is not considered comprehensive in this context.
Note 2: SNOT-22 questionnaire available as Supplementary Material to Kennedy et al. Ann Allergy Asthma Immunol. 2013;111:246-251.e2.
Note 3: Optimised nasal polyps therapy defined as: (a) adherence to intranasal corticosteroid therapy for at least three months prior, unless contraindicated or not tolerated, and (b) nasal irrigation with saline, unless not tolerated or not clinically required, and (c) short-course oral corticosteroids, if required.

Renewal from any relevant practitioner. Approvals valid for 12 months where the treatment remains appropriate and the patient is benefiting from treatment (see Note).
Note: Treatment benefit based on either:

1. Any of the following features: reduced nasal polyp size, reduced need for systemic corticosteroids, improved quality of life, improved sense of smell, reduced impact of co-morbidities (eg asthma); or
2. Improvement in SNOT-22 score of at least nine (Chowdhry et al. Int Forum Allergy Rhinol. 2017;7:1149-55).

11.5. In making this recommendation, the Committee considered:

11.5.1. The high symptom burden of CRSwNP and the substantial (and somewhat underappreciated) impact it has on quality of life (QOL) and health utility, which is on a par with several severe chronic health conditions.

11.5.2. The high unmet health need of people with CRSwNP that recurs despite good medical and surgical management, especially for people with comorbid asthma and NSAID sensitivity who require higher rates of revision surgery.

11.5.3. That mepolizumab reduces CRSwNP symptoms, polyp size and the need for repeat surgery, and substantially improves QOL including sense of smell.

11.5.4. That mepolizumab is a suitable treatment for this population.

Discussion

Māori impact

11.6. The Committee discussed the impact of chronic rhinosinusitis (CRS)/CRSwNP on Māori health areas of focus and Māori health outcomes. The Committee considered that the impact of CRS/CRSwNP on Māori was unclear due to sparse evidence, but that the high burden of asthma on Māori, which is commonly associated with CRS/CRSwNP, was understood and well documented in other meeting records. The Committee considered that the challenges accessing timely surgery in the public health system and the cost associated with accessing surgery in private would likely exacerbate the impacts of CRSwNP for Māori people.

Populations with high health needs

11.7. The Committee discussed the health needs of people with CRS/CRSwNP among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding mepolizumab in this context.

11.7.1. The Committee considered the impact of CRS/CRSwNP on these groups was unclear due to sparse evidence, but that the high burden of asthma among these groups was well known and that asthma is commonly associated with CRS/CRSwNP.

11.7.2. The Committee considered that the challenges accessing timely surgery in the public health system and the cost associated with accessing surgery in private would likely exacerbate the impacts of CRSwNP for these groups.

Health need

11.8. The Committee noted that chronic rhinosinusitis (CRS) affects up to approximately 20% of the population and up to 30% of individuals with CRS have nasal polyps (CRSwNP) (Stevens et al. J Allergy Clin Immunol Pract. 2016; 4: 565–72). The Committee noted that CRSwNP is a Th2 disorder that is typically diagnosed between 40 and 60 years of age and is often associated with other conditions and comorbidities including asthma (in up to 65% of cases) and with aspirin- or nonsteroidal anti-inflammatory- exacerbated respiratory disease (NSAID-ERD, in up

to 26% of cases) (Bachert et al. J Asthma Allergy. 2021;14:127-34). The Committee was made aware of evidence reporting concurrent eczema in 40% of people with CRS; and CRS in 45% of those with eczema (Knudgaard et al. 2021; Ann Allergy Asthma Immun; 127:49-56). Members noted that people with Th2 inflammatory nasal polyps would be distinct from the group targeted by these applications.

11.9. The Committee considered that CRSwNP symptoms have a high impact on quality of life (eg due to nasal congestion, loss of smell and rhinorrhoea) that is somewhat underappreciated by those not involved in treatment of individuals with CRSwNP. The Committee considered that loss of sense of smell is correlated with disease severity and is a major determinant of loss of quality of life (QOL). The Committee noted that QOL endpoints in studies of CRS/CRSwNP use the disease-specific sinonasal outcome test (SNOT-22) instrument or the more general SF-36. The Committee noted evidence of worse bodily pain and social functioning scores in people with chronic sinusitis than those with congestive heart failure, chronic obstructive pulmonary disease (COPD), angina, or sciatica (Gliklich et al. Otolaryngol Head Neck Surg. 1995;113:104-9); and health state utility impairment in CRS being on a par with end-stage renal disease, moderate asthma, Parkinson's disease, and coronary artery disease (Soler et al. Laryngoscope. 2011;121:2672-8).

11.10. The Committee noted that the consumer applicant had highlighted a number of considerations including that the disease's symptoms and surgery both impact the person's ability to maintain and gain employment, that surgery is associated with long waitlists or personal cost for those who can elect to undergo this in private, and that the social stigma associated with COVID-19 like symptoms including loss of smell can also affect people with CRSwNP.

11.11. The Committee considered that standard of care for initial treatment of CRSwNP is with medical interventions including intranasal corticosteroids (INCS), saline rinses, and short courses of oral corticosteroids (OCS). Members considered that adherence to these standard of care treatments is often poor. The Committee noted that endoscopic sinus surgery is considered for disease that is not well controlled by medical treatments, and that comprehensive surgery is effective (both primary surgery and revision for cases of recurrence) in providing substantial improvements in health utility and a greater reduction in polyp size than biologics (Soler et al. 2011; Miglani et al. Int Forum Allergy Rhinol. 2023;13:116-28).

11.12. Members considered that the extent of surgery necessary for nasal polyposis can vary substantially. Members considered that for cases of polyp recurrence despite appropriate medical treatments, initial surgery might be different degrees of functional endoscopic sinus surgery (FESS), while a more comprehensive surgery would include a frontal sinus drill-out. Members considered that standard of care medical treatments are used post-operatively for both approaches, and that subsequent therapies would depend on the time to next recurrence:

- if recurrence occurs after at least one year following comprehensive surgery, then the prior surgery would be considered to have been effective and another revision would be reasonable (with standard of care post-operatively).
- if recurrence occurs within one year following comprehensive surgery, then the use of other medical treatments (eg biologics, if available) would be reasonable. Further surgical revision could also be considered if appropriate.

11.13. Members considered that, based on anecdotal experience, 60-80% of polyps will not recur after well-performed, comprehensive surgery. The Committee noted the supplier application has cited a timeframe of six to 18 months for polyp regrowth post-resection (DeConde et al. Laryngoscope. 2017;127:550-5; Ren et al. World Allergy Organ J. 2019;12:100050), while other evidence reports recurrence rates ranging

from 20% to 60% within 18 months to four years follow-up, up to 79% over a 12-year period (Bhattacharyya et al. Laryngoscope. 2019;129:1969-75; Calus et al. Clin Transl Allergy. 2019:9:30). The Committee was made aware of evidence indicating that a proportion of people would experience up to four sinus operations for CRSwNP (Khan et al. Rhinology. 2019;57:32-42). The Committee noted that people with CRSwNP who have comorbid asthma or NSAID sensitivity are reported to experience higher rates of revision surgery (Bachert et al. 2021).

11.14. The Committee noted that biologics (such as mepolizumab) were proposed as third-line therapies in the supplier's treatment paradigm, but considered that the proposed paradigm omitted those who would not be suitable for surgery (eg due to comorbidities or contraindications to surgery) or those requiring repeat surgery. The Committee considered that biologics would be appropriate for cases of recurrence within one year following comprehensive surgery. The Committee considered that repeat surgery (FESS) may be an appropriate comparator for assessing mepolizumab in this context.

11.15. The Committee considered that surgery for CRSwNP in New Zealand occurred in similar proportions in the public and private health sectors, although public sinus surgery is associated with long waitlists in many locations. The Committee was made aware that some individual surgeons perform about up to ten of these operations per year. The Committee considered that the 'access advantage' with private surgery would not necessarily translate into earlier consideration of, or access to, a biologic therapy given that access to a biologic would be best determined by the timeframe between comprehensive surgery and recurrence.

11.16. The Committee noted that mepolizumab is Medsafe-approved for several indications, including as an add-on treatment in adult patients aged 18 years and above with severe CRSwNP who have received an inadequate response from INCS.

11.17. The Committee noted that dupilumab has not yet been submitted to Medsafe, although its registered indications overseas include the treatment of CRSwNP, asthma and eczema.

11.18. The Committee noted a publication by Han et al. (Laryngoscope. 2022;132:265-71), which reported proposed thresholds for clinically meaningful within-patient change in specific quality of life (QOL) outcome measures using data from the LIBERTY SINUS-24 and -52 trials (see *Dupilumab clinical trial evidence*, below) and using the 22-item SNOT-22 questionnaire, using the rhinologic symptoms domain as an anchor. The Committee was made aware of the following studies that reported the minimal important difference (MID) for changes in efficacy outcomes in CRSwNP patients as follows:

- Nasal polyp score (NPS) reduction of 0.5 and meaningful change threshold (MCT) of 1.0 (Braid et al World Allergy Organ J. 2023;16:100776). The Committee considered a reduction in NPS of 1.0 to be clinically significant.
- SNOT-22 score of 9 (Chowdhry et al Int Forum Allergy Rhinol. 2017;7:1149-55).
- Visual analogue scale (VAS) scores for allergic rhinitis and for total symptoms in hayfever each of 3 (Bousquet et al. J Allergy Clin Immunol. 2009;123:1349-54; Nagino et al. Clin Transl Allergy. 2023;13:e12244) or a 15% improvement in VAS over baseline value with a desirable clinically important difference of 45% (Haye et al. J Laryngol Otol 2023;137:1285-88).

Mepolizumab clinical trial evidence

11.19. The Committee noted that the key evidence for mepolizumab for CRSwNP comes from the phase III, double-blind, randomised (1:1), placebo-controlled SYNPASE trial of mepolizumab compared with placebo in 407 people with CRSwNP who had at

least one prior nasal operation in the past ten years (Han et al. Lancet Respir Med. 2021;9:1141-53). Members considered that the ten-year timeframe suggested a good outcome from prior surgery.

11.19.1. The Committee noted that at 52 weeks follow-up, the total NPS improved with mepolizumab compared with placebo (adjusted difference in medians −0.73, 95% CI: −1.11, −0.34; *P*<0.0001). The Committee noted that the nasal obstruction VAS scores also improved with mepolizumab during weeks 49 to 52 (−3.14, 95% CI: −4.09, −2.18; *P*<0.0001). The Committee noted that the differences in these coprimary endpoints each exceeded their respective MIDs.

11.19.2. The Committee also noted the following outcomes reported from SYNAPSE:

- People receiving mepolizumab were less likely to require further sinus surgery (46 [23%] placebo vs 18 [9%] mepolizumab (hazard ratio 0.43 (95% CI: 0.25, 0.76); *P*=0.0032). The Committee noted that the surgery rate in the placebo group was about 20% at 12 months.
- The adjusted difference in median SNOT-22 score was –16.49 (95% CI: –23.57, –9.42); *P*=0.0032
- The adjusted difference in median VAS score for sense of smell was –0.37 (95% CI: –0.65, –0.08); *P*=0.020
- The adjusted difference in median overall VAS score was –2.68 (95% CI: –3.44, –1.91); *P*=0.020
- There was no meaningful increase in adverse events with mepolizumab vs placebo.

11.20. The Committee noted that VAS scores can be obtained using a scale of one to ten or marking a point on a line, and considered measurement could be subject to clinician influence.

11.21. The Committee noted further publications from the SYNAPSE trial which reported exploratory subgroup analyses (Bachert et al. J Allergy Clin Immunol. 2022;149:1711-21) and post hoc surgical analyses (Fokkens et al. Allergy. 2023;78:812-21; Hopkins et al. Rhinology. 2023 1;61:108-17). The Committee considered that the exploratory subgroup analyses indicated that all subgroups received benefits in terms of risk of surgery, odds of requiring systemic corticosteroids (SCS) and nasal obstruction VAS score. The Committee noted that those with higher blood eosinophil counts (ie ≥300 cells/µL) consistently had a greater likelihood of receiving a benefit.

11.22. The Committee noted that, of those who received clinical benefit at six months, 85% were on treatment at 12 months but the other 15% were not. The Committee considered that with biologics, individuals discontinuing treatment would no longer receive any benefit.

Dupilumab clinical trial evidence

11.23. The Committee noted again that dupilumab had not been submitted to Medsafe at the time of the meeting, and therefore a formal recommendation for funding could not be provided.

11.24. The Committee noted evidence from the LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 trials, which were two multicentre, randomised, double-blind, placebo-controlled, parallel-group studies assessing dupilumab added to standard of care in adults with severe CRSwNP (Bachert et al. Lancet. 2019;394:1638-50). SINUS-24

included 276 participants who received either dupilumab 300mg or placebo every two weeks for 24 weeks. SINUS-52 included 448 participants who received dupilumab 300mg every two weeks for 52 weeks, or dupilumab 300mg every two weeks for 24 weeks then 300mg every four weeks for 28 weeks, or placebo for 52 weeks. All groups received standard therapy (INCS) alongside their assigned treatment.

11.24.1. The Committee noted that dupilumab improved NPS and nasal congestion score (NCS) coprimary endpoints at 24 and 52 weeks compared to placebo which had no difference in NPS and little change in NCS; the least squares mean differences vs placebo for these endpoints were statistically significant at both timepoints (all $P<0.0001$ and 95% CIs did not cross zero).

11.24.2. The Committee noted that people administered dupilumab in the SINUS studies had a reduced need for repeat surgery vs placebo (pooled proportion requiring SCS or sinonasal surgery: 97/286 [34%] placebo vs 42/438 [10%] mepolizumab at 52 weeks; hazard ratio vs placebo 0.243 (95% CI: 0.169, 0.351; $P<0.0001$).

11.24.3. The Committee noted that after six months, dupilumab every two weeks was reported to be just as effective (or slightly more so) than dupilumab four-weekly in terms of NPS and nasal congestion or obstruction. The Committee considered that in practice, two-weekly dosing might occur for the first six months with ongoing dosing given four-weekly, although data comparing time to first corticosteroid use or time to nasal surgery for the two dupilumab regimens would be required to fully assess the differences between them.

11.25. The Committee was made aware of evidence reporting either no difference in outcomes with dupilumab according to baseline eosinophil count (De Corso et al. Allergy. 2023;78:2669-83) or increased efficacy in individuals with greater blood eosinophil counts (Ryser et al. Allergy. 2023;78:2712-23). However, the Committee was also made aware that some European approvals and recommendations require evidence of Th2 inflammation for dupilumab, such as an elevated blood eosinophil count.

General comments on evidence

11.26. The Committee also noted the applicant-provided evidence and evidence identified by Pharmac staff literature searches.

11.27. The Committee noted that there are no head-to-head trials comparing mepolizumab and dupilumab. The Committee noted that many studies positioned surgery as the likely comparator. The Committee noted that the clinical trials included people who received multiple operations, but considered that there is no evidence that this affected the effectiveness of biologic therapy. The Committee considered that the evidence is generalisable to the New Zealand context, noting that concurrent treatments used in the trials were similar.

11.28. The Committee noted a meta-analysis of seven studies involving 799 patients receiving mepolizumab (including SYNAPSE), benralizumab, or reslizumab (Wang et al. Int Arch Allergy Immunol. 2022;183:732-43). The Committee noted that the authors reported that mepolizumab reduced polyp size and improved QOL and NCS.

11.29. The Committee noted that the Cochrane meta-analysis of biologics for CRS by Chong et al. (Cochrane Database Syst Rev. 2021;3:CD013513) assessed two studies in people administered mepolizumab (N=137) and three studies involving dupilumab (N=784). The authors reported a reduction in SNOT-22 at 24 weeks (-19.61, 95% CI: -22.54 to -16.69) and a reduction in disease severity (using VAS global symptom score) at 16-52 weeks (MD -3.00, 95% CI: -3.47 to -2.53) with dupilumab. The authors report that with mepolizumab, SNOT-22 may be reduced at

25 weeks (-13.26, 95% CI: -22.08 to -4.44) and it was very uncertain if there is a difference in disease severity at 25 weeks due to the very small sample size for this outcome (n=72) and the absence of evidence that a validated tool was used (VAS -2.03 lower with mepolizumab, 95% CI: -3.65 to -0.41).

11.30. The Committee noted a network analysis indirectly comparing dupilumab, mepolizumab, omalizumab and benralizumab based on seven randomised controlled trials with some heterogeneity among them (Cai et al. J Allergy Clin Immunol Pract. 2022;10:1876-86.e7). The Committee considered that the results indicated that all of these biologic treatments are more effective than placebo in decreasing NPS, NCS and SNOT-22 score.

11.31. The Committee noted a prospective, multicentre, non-randomised study comparing FESS with biologic therapy for severe CRSwNP (Miglani et al. Int Forum Allergy Rhinol. 2023;13: 16-28). The Committee noted that FESS provided comparable improvements in QOL (SNOT-22) and smell identification at 24 weeks compared with dupilumab. The Committee noted that FESS offered significantly greater reductions in polyp size compared to omalizumab, dupilumab, and mepolizumab, and considered this reinforced the view that biologics should be considered for recurrence post-surgery.

11.32. The Committee considered that there may be some increased risk of lymphoma with biologics for CRSwNP, as evidenced for omalizumab, and that dupilumab may be associated with a rare but increased risk of hypereosinophilia.

Suitability

11.33. The Committee considered that some centres may have a standard process for training patients and their families/caregivers on injection technique, but that some people may not be able to self-administer at all for individual reasons. The Committee considered that doses given by healthcare providers in primary care would likely require the patient to pay a fee for the administration of each dose.

Cost and savings

11.34. The Committee considered that there would be low uptake initially, but this would increase. The Committee considered that people with CRSwNP targeted by the application would require lifelong treatment with biologics. The Committee considered that some people may stop treatment due to inconvenience or pain, but that the majority would remain on biologic treatment irrespective of whether repeat surgery is undertaken.

11.35. The Committee considered the supplier suggestion that uptake may increase at the same rate each year to be reasonable, as a set number of patients will be able to access specialists and gain access, then would stay on treatment indefinitely for as long as renewal criteria are met. This would be similar to individuals accessing mepolizumab for asthma. The Committee considered the number of patients ceasing therapy would be higher than for those treated for asthma, but the exact proportion was unknown.

11.36. The Committee considered that if mepolizumab were funded for CRSwNP there would be some crossover with asthma usage for severe eosinophilic asthma and eosinophilic granulomatosis. However, the Committee considered that individuals would be more likely to access mepolizumab for severe asthma rather than for CRSwNP, if both conditions were present. Members considered it reasonable to estimate 40-50% with CRSwNP would also have asthma, and a maximum of 10% may already be receiving a biologic for severe asthma.

11.37. The Committee considered that biologics switching would need to be considered if multiple biologics were funded for CRSwNP.

Funding criteria

11.38. The Committee considered that the Special Authority criteria should specify one comprehensive operation has been undertaken previously (including a frontal sinus drill-out), as surgery needs to be comprehensive to achieve optimal outcomes. Members suggested a recurrence at one year following the most recent comprehensive surgery was reasonable for targeting people to access biologics.

11.39. The Committee considered it appropriate for funded treatment with a biologic for CRSwNP to include the very small proportion of people who are not candidates for nasal surgery.

11.40. The Committee considered that it was reasonable to exclude those with other causes of polyps or other reasons for nasal surgery, for whom biologics would not be suitable, from the target population for funding.

11.41. The Committee noted that the supplier-proposed Special Authority criteria used NPS and VAS scores, which are used to determine eligibility in the clinical trials. The Committee considered that criteria reflecting the presence of symptoms would be more accurate and practical than a number based on NPS or VAS scores, noting that VAS scores could be subject to clinician influence and the scale would need to be obtained by a clinician during a clinical assessment. However, Members considered that if a scale-based assessment were to be used then the SNOT-22 would likely be more accurate than a VAS.

11.42. The Committee considered that appropriate renewal criteria to include in the draft Special Authority were unclear, noting that requiring surgery would not necessarily stop treatment with a biologic (as requiring surgery would not always mean the biologic was no longer effective) and the clinical trials only provided one year of follow up data. However, the Committee considered that it may be reasonable to incorporate the five criteria used in the European Position Paper on Rhinosinusitis and Nasal Polyps (2020) (Fokkens et al. Rhinology. 2020;58(Suppl S29):1-464) to gauge whether there is ongoing benefit from treatment.

Summary for assessment

11.43. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for mepolizumab if it were to be funded in New Zealand for CRSwNP. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) with: ○ Uncontrolled symptoms despite optimised therapy including persistent use of intranasal corticosteroids (INCS) ○ At least 1 prior comprehensive nasal polyp operation (which includes a frontal sinus drill-out) ○ Recurrence occurred within one year following comprehensive surgery ○ Eosinophil count ≥300 cells/μL
Intervention	Standard of care (as below, including repeat functional endoscopic sinus surgery [FESS] if necessary) plus add-on therapy of mepolizumab; one 1ml subcutaneous injection pen (100mg/ml) every four weeks.

Comparator(s)	Standard of care includes: ○ INCS ○ Short courses of oral corticosteroids (OCS) ○ Saline rinses ○ Repeat FESS if necessary
Outcome(s)	• Improvement in overall quality of life (QOL) • Improvement in sense of smell • Reduction in polyp regrowth • Reduction of 57% in the need for surgery over 52 weeks • Reduction of 43% in use of OCS (Reductions in surgery and OCS use as reported from the SYNAPSE trial; Han et al. Lancet Respir Med. 2021;9:1141-53)
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.	

Chair

Date