Record of the Respiratory Advisory Committee Meeting held on 27 April 2022

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

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.

Specialist 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.

PTAC 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 PTAC 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.

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1. Attendance

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

Apologies:
Tim Stokes

2. Summary of recommendations

2.1. The following recommendation summary is in order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• **ELX/TEZ/IVA** for the treatment of people with cystic fibrosis, who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene	**High Priority**
• Widening of access to **ivacaftor** for the treatment of cystic fibrosis to patients with the mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, 711+3A→G, 2789+5G→A, R117C, 3272-26A→G, S945L, 3849+10kbC→T, S977F, L206W, A455E, R347H, R352Q, D579G, D1152H, P67L, R1070W, and E831X	**High Priority**
• Widening of access to **mepolizumab** for the treatment of relapsed or refractory eosinophilic granulomatosis with polyangiitis with a high priority	**High Priority**
• **Adrenaline auto-injector** for the emergency treatment of anaphylaxis in the community	**High Priority**
• Widening of access to **nintedanib** for patients with PFILDs	**High Priority**
• Widening of access to **pirfenidone** for patients with PFILDs	**Medium Priority**
• Widening of access to **pirfenidone** to include the subgroup of patients with PFILDs for whom nintedanib is not tolerated, if access to nintedanib for PFILD were widened	**High Priority**

3. The role of PTAC 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) and Specialist Advisory Committees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

3.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Advisory Committees and PTAC.

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

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

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

4. Therapeutic Group and NPPA Review

Discussion

Funding decisions and applications

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

4.1.1. The Committee noted the decision to fund benralizumab, with listing to occur following Medsafe approval for the prefilled pen presentation. The Committee noted Pharmac's intention was to harmonise the criteria for mepolizumab and benralizumab for the treatment of severe eosinophilic asthma, to enable flexibility for clinicians and patients to choose the most appropriate first line agent. The Committee noted patients would be able to transition to the alternative treatment if they received an insufficient response within 12 months of starting treatment.

4.2. The Committee noted the outstanding funding applications in the respiratory and allergies therapeutic group.

4.2.1. The Committee considered it may be beneficial to review the TOBI podhaler application. The Committee noted that PTAC had previously recommended funding of the TOBI podhaler for people with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection subject to a cost neutral proposal (accounting for the offsets to

the healthcare sector). The Committee highlighted that there are additional costs associated with inhalation of the solution, as this requires consumables such as nebulisers and equipment. Equipment such as a nebuliser bulb was dispensed to a patient each year. However, these items were likely being provided by DHB hospital departments without specific funding and done inconsistently and perhaps inequitably across the country. The Committee considered it important that Pharmac considered these costs in its assessment.

4.2.2. The Committee noted an application for dupilumab for the Maintenance treatment of patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) had been received in August 2021, however there was no product with regulatory approval in New Zealand. The Committee considered it may be beneficial for Pharmac staff to engage with the supplier of dupilumab, noting it also has uses in dermatology.

4.2.3. The Committee noted Trikafta was a separate discussion item on the agenda.

4.3. The Committee noted a funding application had been received for palivizumab for the prevention of respiratory syncytial virus (RSV).

4.3.1. The Committee also noted the draft record of PTAC's discussion in February 2022. The Committee considered that there was uncertainty regarding the timings and impacts of the upcoming RSV season and considered time-bound funding was appropriate in the context of COVID-19. Members considered the assessment of the cost-utility of palivizumab in other jurisdictions prior to COVID-19 demonstrated variable and often poor cost-effectiveness.

4.3.2. The Committee considered the main benefit of palivizumab was in preventing hospitalisation and that its use in infants already in hospital had limited cost-effectiveness. Members considered hospital policies and procedures were usually effective and had become more effective in recent times to prevent the impact of an outbreak.

4.3.3. The Committee highlighted that children over 12 months who were still dependent on ventilation/respiratory support in the community were at very high risk of severe RSV-related illness and should be considered in the eligibility criteria.

<u>NPPA</u>

4.4. 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 via the Schedule and/or were due to be discussed at the meeting. No other medicines were raised as options for consideration via the Schedule funding process.

<u>Respiratory inhalers</u>

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

Asthma guideline updates

4.6. The Committee considered Pharmac staff's estimates regarding the relative proportions of patients receiving SABA therapy to be reasonable. The Committee considered the 2020 updates to the New Zealand Adolescent and Adult Asthma Guidelines would continue to increase the dispensing of budesonide with eformoterol inhalers, and considered it likely that budesonide with eformoterol inhalers prescribing would increase, with a reduction in market share of Vannair and Duoresp products.

Members indicated some older children and adolescents with asthma on an AIR regimen preferred the Duoresp Spiromax over the Symbicort Turbuhaler products.

4.7. The Committee considered the increase in budesonide with eformoterol usage would likely increase at a slower rate than previously seen since the guidelines changes. The Committee considered there had been rapid uptake following the changes to the guidelines and remaining practitioners would likely be slower to adopt the changes. However, overall, the number of patients to change to the AIR therapy regimen would not change from previous estimates.

4.8. Members considered it would be beneficial for Pharmac staff to review usage of dry powder inhalers (DPIs) in this area however, considered the changes to the guidelines would be unlikely to affect adoption of DPIs.

Budesonide/formoterol stat dispensing

4.9. The Committee considered it would be reasonable to limit the number of inhalers each person could receive per dispensing to avoid anticipated wastage, if changing the schedule to allow stat dispensing. The Committee considered most people would require approximately three inhalers per stat dispensing (eg one per month).

4.10. The Committee also noted however that some people would require up to 9 per dispensings (noting the SMART regimen includes a maximum dose of 12 inhalations per day, equating to 9 inhalers in a three-month period). Therefore, any dispensing limits would need to allow for some patients to receive a greater number than three per dispensing over a three-month period. The Committee considered that to enable access to greater than 3 inhalers via stat dispensing, it may be appropriate to add an endorsement to the criteria for budesonide with eformoterol.

4.11. The Committee considered the mechanism to limit the number of inhalers dispensed (eg restrictions) needed to be carefully considered, in order to minimise barriers for patients.

COPD guideline introduction

4.12. The Committee considered it likely that the introduction of COPD guidelines would continue to increase the dispensing of LAMA/LABA inhalers. However, the Committee considered the uptake would not likely be as steep as expected from the historical data, as the prescribing of combination inhalers is already common practice.

LAMA/LABA market dynamics

4.13. The Committee considered that within each class (LAMA or LAMA/LABA), the agents are of same or similar clinical effect. The Committee considered the key differences are likely to be related to device preference.

4.14. The Committee did not identify any clinical issues with reducing the number of available funded inhaler options in the LAMA or LAMA/LABA subgroups (eg down to two). However, the Committee considered there is very strong user preferences in the inhaler markets and that suitability of products would need to be a key consideration.

4.15. The Committee considered people could transition between therapeutic agents, provided devices are acceptable to the individual and the side effect profiles are manageable. However, the Committee highlighted that it was likely that patients would prefer to switch between subgroups in order to remain on the inhaler product type (eg

Ellipta or Breezhaler series) rather than to a different chemical in the same subgroup. The Committee considered that this may result in unanticipated costs and may limit the financial benefits of reducing the number of inhalers in each class.

4.16. The Committee considered the primary risk would be that some people required to transition to a new inhaler may not be trained sufficiently and therefore experience a worsening of symptoms and risk deterioration. The Committee considered there was a small risk clinically with moving from LAMA or LABA alone to an ICS combination inhaler, given the risks associated with ICS use.

4.17. The Committee considered several patient groups would require additional support if a brand or chemical change were to occur, including children with asthma (where both children and caregivers need to be taught appropriate techniques) and elderly patients. The Committee highlighted it can take multiple education sessions and reinforcement to teach and embed proper inhaler technique, in order to support responsible and 'good' use of prescribed inhalers. This cost to the healthcare system should be considered as part of any future work.

4.18. The Committee considered there may be benefit in further consideration of the LAMA/LABA market dynamics, with more detailed usage information provided to the Committee to support further discussion.

4.19. The Committee considered data from other jurisdictions would be useful in determining the long-term role of triple ICS/LABA/LAMA therapy inhalers in the treatment of asthma and COPD. Members considered triple therapy inhalers were adopted relatively easily, however had some risks of over-medicating people who do not require all three components (particularly given the fixed ICS component).

4.20. The Committee considered further education of prescribers regarding inhalers (both appropriate prescribing and inhaler technique) would be beneficial.

Budesonide in COVID-19 guidelines

4.21. The Committee considered the use of inhaled budesonide for the treatment of COVID-19 would decrease, in line with the reduction in COVID-19 in New Zealand. The Committee considered there was uncertainty regarding its future usage however, given the recent inclusion of budesonide in the New Zealand COVID-19 advice to health professionals.

Environmental impact of inhalers

4.22. The Committee noted a funding application had been received for a salbutamol DPI and Pharmac staff were seeking the Committee's initial views.

4.23. The Committee noted metered dose inhalers (MDIs) were associated with a significant climate change potential and that there was an ongoing drive internationally to move to DPIs, which have a substantially lower carbon footprint. The Committee considered some DPIs and the required technique are more challenging to use than some of the MDI comparators, which may limit DPI uptake.

4.24. The Committee noted there was ongoing research into changing the propellant in MDIs to a more environmentally responsible option. Soft mist inhalers (SMIs) were also growing in popularity in other jurisdictions as a more environmentally responsible inhaler.

4.25. The Committee considered it important to monitor global trends in order to ensure that New Zealand did not fall 'out of step' with other jurisdictions, which could result in future supply issues. Members considered changes to legislation in regions such as the European Union would likely drive changes.

4.26. The Committee was not aware of any differences in efficacy between MDIs and DPIs when used correctly. However, incorrect use can easily result in a difference in efficacy. The Committee considered listing a salbutamol DPI would provide people with choice, without having to change to a different SABA agent (eg terbutaline).

4.27. The Committee considered Pharmac should take into account the associated cost of spacers with MDIs when considering any commercial proposals for DPIs or SMIs. The Committee considered there were a range of groups for whom DPIs may be inappropriate. The Committee considered SMIs would be appropriate for all these patient groups, as follows.

4.27.1. There is a niche use of MDIs for intubated people, for whom a DPI would not be appropriate.

4.27.2. Some people with asthma or COPD may not produce high enough inspiratory flow rates during an exacerbation for DPI use to be effective.

4.27.3. DPIs cannot be used by small children, and even older children can struggle to use these devices appropriately.

4.27.4. People with an intellectual disability who may need additional support in learning inhaler technique.

4.27.5. Pulmonary function labs use MDIs and spacers, otherwise a new inhaler would be required for every individual.

4.28. Members considered a shift in practice would be required for DPIs to be used in the treatment of acute severe asthma in ED.

4.29. The Committee considered patient and clinician preference would shift with the growing awareness of the environmental impact of inhalers. Pharmac could support this by phasing out HFA inhalers in the long term (noting this is likely to happen anyway based on the global trends in the inhaler markets). However, unless a valid alternative is available, the Committee considered it would be inappropriate to undertake any work that may create anxiety in inhaler use among patients that results in negative clinical outcomes (eg the cessation of treatment due to concerns over environmental impact without a funded alternative).

<u>Omalizumab and mepolizumab</u>

4.30. The Committee considered usage of omalizumab would slow from the uptake rate since listing, given the funding of mepolizumab. The Committee considered the recent funding and impending listing of benralizumab would be unlikely to change the usage of omalizumab.

4.31. The Committee considered the usage of mepolizumab would continue to increase and that COVID-19 may have delayed treatment initiation for some people who meet the eligibility criteria. The Committee considered its previous uptake estimate of 500 people to be a reasonable assumption, however noted this would be split between mepolizumab and benralizumab (once listed). The Committee considered

mepolizumab may have a greater market share given it was listed first and therefore has greater familiarity among clinicians and patients.

4.32. The Committee indicated there was emerging evidence to support the use of mepolizumab in children aged 6-12 and considered it likely Pharmac would receive a funding application once more evidence is available.

Antibiotics for bronchiectasis

4.33. The Committee noted the available antibiotic options for non-cystic fibrosis bronchiectasis were limited compared to those available for people with cystic fibrosis. The Committee considered people with non-cystic fibrosis bronchiectasis would gain similar health benefit from anti-infective treatments (ie ceftriaxone, colistin sulphomethate, gentamicin sulphate, tobramycin, vancomycin and azithromycin) as to those with cystic fibrosis. The Committee indicated non-cystic fibrosis bronchiectasis disproportionately impacts Māori and people living in areas of low socio-economic status. The Committee considered Māori and Pacific peoples were over-represented in people presenting with severe bronchiectasis and considered widened access would have substantial equity benefits for these populations. The Committee acknowledged that the overall health need of people with cystic fibrosis was usually higher, given the other impacts of cystic fibrosis (ie increased morbidity and mortality).

4.34. The Committee noted the concerns regarding antibiotic resistance for azithromycin raised by the Anti-Infectives Advisory Committee. However, the Committee considered azithromycin is being used as an immunomodulator and had evidence out to 24 months to support its use. The Committee considered screening for atypical mycobacteria to exclude atypical infection was a standard part of management and reduced the risk of increasing antibiotic resistance. The Committee considered the concerns from the Anti-Infectives Advisory Committee was in relation to a much larger population (use in all bronchiectasis cases) whereas there was opportunity to specify a more severe subgroup. The Committee considered exacerbation rates in those over 18 could be an appropriate criterion to restrict access to those who would benefit most.

4.35. The Committee indicated that some agents funded in hospital as an IV solution were dispensed in hospital for nebulised community use, to provide funded access to people without cystic fibrosis requiring treatment. Therefore, the Committee considered widening access could in effect shift funding from hospital to community. The Committee noted such use of these agents via nebuliser did come with a risk of bronchospasm.

Horizon scanning

4.36. The Committee noted the previous agents identified through horizon scanning. The Committee reiterated the potential treatments in the pipeline for RSV prevention.

4.37. The Committee considered the following treatments to be of interest, some of which had already been submitted for consideration via funding application:

- Mepolizumab for severe eosinophilic asthma for children over the age of 6 years
- Treatments for non-cystic fibrosis bronchiectasis
- Fexofenadine as a non-sedating antihistamine

- Low dose morphine tablet or immediate release 5 mg tablet
- Macitentan for pulmonary arterial hypertension, in place of bosentan
- Sodium oxybate for narcolepsy
- Palliative care medicines such as ketamine and lidocaine.

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

Application

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

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

Recommendation

5.3. The Committee **recommended** that no changes be made to its previous recommendation, where it had recommended that ELX/TEZ/IVA be listed with a **high priority** within the context of treatment of respiratory disease, subject to the following Special Authority criteria:

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

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

Note

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

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

Discussion

5.5. The Committee noted that it had previously reviewed an application for ELX/TEZ/IVA at its August 2021 meeting, where it was recommended for funding with a high priority for those with cystic fibrosis (CF) who were aged six years and older. The Committee noted that the application was subsequently reviewed by PTAC at its November 2021 meeting where it was recommended for funding with a medium priority for those patients aged 12 years and over, but a recommendation was deferred for those patients aged 6 to 11 years and for those with mutations for which only *in vitro* data showing responsiveness to ELX/TEZ/IVA is available, pending further data. The Committee noted that PTAC had recommended that further advice be sought from the Respiratory Advisory Committee regarding the appropriateness of inclusion of renewal (or stopping) criteria in the Special Authority criteria, and whether a phenotypic definition of CF may be a more appropriate than genotypic criteria for access.

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

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

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

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

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

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

Ethnic variation and phenotypic eligibility criteria

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

evidence would further broaden the eligible patient population and thus help address any issues of inequity in this patient group.

5.10. The Committee noted that there are two main routes to diagnosis of CF. Firstly, population-wide newborn Guthrie screening detects about 90% of cases, which the Committee considered to be a comprehensive strategy for identifying the more common mutations. The Committee noted secondly that remaining patients who become symptomatic later in life would have phenotypic testing via a sweat chloride test in the first instance followed by genetic testing. The Committee considered that while genetic testing is relatively accessible for CF patients throughout New Zealand, sweat chloride testing accessibility is variable, and some patients may have to travel distances to access testing. The Committee considered that CF diagnosis in New Zealand is comprehensive, and that almost all patients will be included in the NZ CF registry. The Committee considered that it is unlikely that the Māori CF patient population are underrepresented, due to the breadth of newborn screening in New Zealand but considered that Māori patients living rurally may encounter barriers to accessing sweat chloride testing.

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

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

Renewal criteria

5.13. The Committee noted PTAC's recommendation that advice be sought regarding the appropriateness of renewal criteria (or stopping) criteria for patients not benefiting from treatment with ELX/TEZ/IVA. The Committee considered that re-evaluation to confirm benefit before transitioning patients to a lifetime of treatment on ELX/TEZ/IVA would

not be appropriate. The Committee considered it would be difficult to identify a group for which this could apply, as all potential response measures are somewhat variable for individuals and that renewal criteria would not be able to effectively incorporate the prevention of progression of CF versus clinical benefit from baseline, especially in younger patients or those who do not have severe disease prior to initiation of ELX/TEZ/IVA treatment.

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

Mutations with in vitro *evidence of efficacy*

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

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

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

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

ELX/TEZ/IVA. The Committee considered that this had been effectively achieved for access to dornase alfa previously.

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

Eligibility of patients aged less than 12 years of age

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

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

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

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

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

Lung function decline and long-term efficacy

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

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

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

Additional observational evidence supporting efficacy of ELX/TEZ/IVA

5.28. The Committee noted that the supplier had provided information regarding the first interim analysis of a 5-year ongoing post-authorisation safety study (PASS) of ELX/TEZ/IVA. The Committee considered that some of the results from the study would have been confounded by the COVID-19 pandemic preventing in-person clinical evaluations, as well as general improvements in best supportive care over time. The Committee noted that the 'real-world' non-experimental observational results reported similar efficacy to that seen in clinical trials across genotypes and considered that this was impressive as the magnitude of effects observed in clinical trial results are rarely reproduced in real-world setting. The Committee noted that the study reported lower prevalence of airway pathogens, increases in ppFEV1 and BMI, and decreased hospitalisation, exacerbations, transplant, and death.

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

6. Ivacaftor for the treatment of cystic fibrosis – widening access for additional mutations

Application

6.1. The Advisory Committee reviewed the application for the widening of access to ivacaftor for additional mutations in the treatment of cystic fibrosis.

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

Recommendation

6.3. The Advisory Committee recommended widening of access to ivacaftor for the treatment of cystic fibrosis to patients with the mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, 711+3A→G, 2789+5G→A, R117C, 3272-26A→G, S945L, 3849+10kbC→T, S977F, L206W, A455E, R347H, R352Q, D579G, D1152H, P67L, R1070W, and E831X with a **high priority** within the context of treatment of respiratory disease subject to the following Special Authority criteria:

> Special Authority for Subsidy - PCT only - Specialist
> **Initial application** only from a respiratory specialist or paediatrician. Approvals valid without renewal unless notified for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with cystic fibrosis; and
> 2. Patient must have at least one mutation on the list of CFTR mutations that produce CFTR protein and are known to be responsive to ivacaftor**; and
> 3. Patients must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis or by Macroduct sweat collection system; and

4. Treatment with ivacaftor must be given concomitantly with standard therapy for this condition; and
5. Patient must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing treatment with ivacaftor; and
6. The dose of ivacaftor will not exceed one tablet or one sachet twice daily; and
7. Applicant has experience and expertise in the management of cystic fibrosis.

** Mutations listed in Table 3 of the full prescribing information for ivacaftor found here

6.4. The Advisory Committee made this recommendation based on the evidence of benefit for patients with rare mutations for which clinical trial data is unlikely to be forthcoming, and who have a high health need.

Discussion

6.5. The Committee noted that ivacaftor was funded in February 2020 for people with cystic fibrosis (CF) and G551D or other gating (class III mutation) in the CFTR gene, subject to Special Authority criteria. The Committee noted an application to widen access to ivacaftor to CF patients with residual function mutations shown to be responsive to ivacaftor which are not currently funded. The Committee noted that current eligibility criteria exclude some CF patients who would benefit from ivacaftor.

6.6. The Committee noted that the severity of CF varies from patient to patient and is dependent on the type of mutation present, although patients with the same genotype may have markedly different presentation and progression of disease. The Committee noted that those with residual function mutations often have slower progressing disease than other types of mutations. The Committee noted that there are over two thousand recognised mutations of the CFTR gene, which can also be impacted or modified by polymorphisms on non-CFTR genes. The Committee noted that this can affect the severity of the CF presentation from patient to patient and considered that these polymorphisms may be the cause of some patients with “mild” CF causing mutations presenting with severe symptoms.

6.7. The Committee considered it unlikely that patients with the requested mutations would have a higher rate of lung transplant than those of other patient groups already considered for ivacaftor and ELX/TEZ/IVA. The Committee considered that these patients may also have lower rates of pulmonary exacerbations but noted that this is highly variable from patient to patient.

6.8. The Committee noted that the FDA (USA) has expanded access to ivacaftor to CF patients with mutations with evidence of efficacy in both clinical studies and *in vitro* data and that the mutations are listed in the prescribing information for ivacaftor. The Committee noted that all of the mutations listed in the widening of access application are included in the FDA list of mutations.

6.9. The Committee noted that ivacaftor is Medsafe approved for use in patients with the R117H mutation, a class IV mutation, and noted that ivacaftor is not currently funded for patients with this mutation. The Committee also noted that ivacaftor is Medsafe approved for treatment of CF in patients aged 12 months and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.The Committee noted data from the PORT NZ CF registry indicates that there are 93 patients in New Zealand with a yet uncharacterised mutation. The Committee considered that some of these patients

may have a class II mutation which would make them eligible for treatment with ivacaftor if access were to be widened.

6.10. The Committee noted that, if all access were widened to all mutations requested, an additional 38 patients would be eligible for treatment with ivacaftor according to CF registry data (excluding the 93 uncharacterised CF patients); nine patients with yet unfunded gating mutations, and 29 patients with the R117H mutation.

6.11. The Committee noted the KONDUCT trial (Moss et al. Lancet Respir Med. 2015;3:524-33) a 24-week, placebo-controlled, double-blind, randomised clinical trial, which enrolled 69 patients with cystic fibrosis aged 6 years and older with R117H and a class II mutation, with percentage of predicted forced expiratory volume (ppFEV1) of at least 40. The Committee noted that at 24 weeks the treatment difference in mean absolute change in ppFEV1 between ivacaftor (n=34) and placebo (n=35) was 2.1 percentage points (95% CI -1.13 to 5.35; p=0.20) which the Committee considered to be expected as younger patients do not have significant pulmonary damage yet. The Committee also noted that treatment with ivacaftor resulted in significant treatment differences in sweat chloride (-24.0 mmol/L, 95% CI -28.01 to -19.93; p<0.0001) and CFQ-R respiratory domain (8.4, 95% CI 2.17 to 14.61; p=0·009).

6.12. The Committee noted the KONNECTION trial (De Boek et al. J Cyst Fibros. 2014;13:674-80) a two-part, randomised, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutations. The Committee noted that for the overall population of the 9 mutations studied, treatment with ivacaftor compared to placebo resulted in significant improvement in ppFEV1 [10.7 through Week 8 (P<0.0001)], BMI [0.66 kg/m2 at Week 8 (P<0.0001)], and CFQ-R respiratory domain score [9.6 through Week 8 (P=0.0004)].

6.13. The Committee noted that sweat chloride is not a measure of CF severity and considered that the 60 mmol cut off in the access criteria is somewhat arbitrary. The Committee noted that some patients may have borderline or normal sweat chloride still experiencing moderate to severe lung disease, but considered that this is not common.

6.14. The Committee noted data from the PORT NZ CF registry indicates that there are 93 patients in New Zealand with cystic fibrosis with a yet uncharacterised mutation. The Committee considered that some of these patients may have a class II mutation which would make them eligible for treatment with ivacaftor if access were to be widened.

6.15. The Committee noted the importance of early initiation of treatment in order to preserve lung function as discussed at this meeting in relation to ELX/TEZ/IVA and considered that this applies to all treatment with CFTR modulator therapies including ivacaftor.

6.16. The Committee considered that Pharmac's exceptional circumstances framework would provide reasonable means for patients with rare mutations to trial ivacaftor. The Committee considered that this had been effectively achieved for access to dornase alfa previously.

6.17. The Committee considered that the strength and quality of evidence for the use of ivacaftor in the treatment of CFTR mutations which are not currently funded was good, particularly given the rarity of the mutations under consideration. The Committee considered that ivacaftor would be effective in patients with the requested residual function mutations regardless of F508del status, as response to ivacaftor is dependent on the presence of the residual function mutations. The Committee considered that it

would be appropriate to extrapolate benefit (acute improvement in lung function, pulmonary exacerbation reduction etc) received by the currently funded population (ie those with a G551D or gating mutation) to those under consideration for widening of access.

6.18. The Committee noted that there are ongoing studies regarding the impact of CFTR modulator therapies on the use of best supportive care practices but considered it likely that patients would need less of their current best supportive care, but not stop all BSC completely. The Committee also considered that funding of CFTR modulator therapies for more CF patients would result in health sector savings such as reduced nursing cost attributed to CF. The Committee noted, however, that children with CF who initiate treatment with CFTR modulators would require additional optometry checks for cataracts.

6.19. The Committee noted that subgroup analyses of ppFEV1 from the Rowe et al. trial all favoured tezacaftor/ivacaftor, especially for patients under the age of 18, where the absolute change in ppFEV1 was 12.0 (95% CI 9.3 to 14.8) versus placebo. The Committee also noted that in subgroup analysis comparing ivacaftor alone with placebo, absolute change in ppFEV1 favoured ivacaftor for all subgroups, but noted that these results were not a strong as for tezacaftor/ivacaftor.

6.20. The Committee noted that there is also evidence of efficacy for the requested CF mutations for Symdeko, a film coated tablet which includes a morning dose of 100 mg of tezacaftor and 150 mg of ivacaftor and an evening dose of 150 mg of ivacaftor. The Committee noted that Symdeko is Medsafe approved for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence, including the mutations sought in the application to widen access to ivacaftor. The Committee noted Symdeko is funded in Australia for patients with at least one residual function mutation, or those homozygous for the F508del mutation, who are 12 years or older, and that no funding application has been made to Pharmac at this time. The Committee noted that in Australia the PBAC noted that no clinical data for patients with an RF mutation without an F508del mutation in the CFTR gene was available for Symdeko, however, the PBAC acknowledged that obtaining efficacy data through a clinical trial would be difficult given the individual rarity of these CFTR genotypes.

6.21. The Committee noted that the submission for Symdeko to the PBAC for this patient population was based on one head-to-head trial, Study 108 (N=244) comparing tezacaftor/ivacaftor plus best supportive care (BSC) with ivacaftor plus BSC and placebo plus BSC in patients aged 12 years and older who are heterozygous for the F508del-CFTR mutation and a second allele with a CFTR mutation predicted to have RF (Rowe et al. N Engl J Med. 2017;377:2024-35). The Committee noted that the least squares (LS) mean treatment difference in ppFEV1 versus placebo from study baseline to the average of week 4 and week 8 was 6.8 (95% CI 5.7 to 7.8) percentage points (P<0.001) for tezacaftor-ivacaftor and 4.7 (95% CI 3.7 to 5.8) percentage points (P<0.001) for ivacaftor. The Committee also noted that for the CFQ-R respiratory domain score, the LS mean change from study baseline to the average of week 4 and week 8 was 11.1 (95% CI 8.7 to 13.6) points for tezacaftor-ivacaftor and 9.7 (95% CI 7.2 to 12.2) points for ivacaftor compared with placebo (P <0.001 for both treatment groups). The Committee noted that sweat chloride concentrations were reduced in patients receiving tezacaftor-ivacaftor and ivacaftor compared with those on placebo (LS mean: tezacaftor-ivacaftor, −9.5 mmol/L [95% CI −11.7 to −7.3]; and ivacaftor,

−4.5 mmol/L [95% CI −6.7 to −2.3]) achieving a mean [SD] of −59.4 mmol/L [29.2] in the tezacaftor-ivacaftor group.

6.22. The Committee considered that in the current setting where only ivacaftor is funded, the Committee would encourage a funding application for TEZ/IVA. The Committee considered that if ELX/TEZ/IVA were funded however, there would not remain an unmet need for TEZ/IVA.

6.23. The Committee considered that although ivacaftor and ELX/TEZ/IVA were both given a high priority recommendation at this meeting, some members considered that the preferred CFTR modulator was ELX/TEZ/IVA due to stronger evidence of benefit than ivacaftor. Members noted that if ELX/TEZ/IVA were to be funded, there would still be a role for ivacaftor in the treatment of a small number of cystic fibrosis patients.

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

Population	Eligible CF patients with a 711+3A→G, 2789+5G→A, R117C, 3272-26A→G, S945L, 3849+10kbC→T, S977F, L206W, A455E, R347H, R352Q, D579G, D1152H, P67L, R1070W, and E831X, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R, R117H mutations
Intervention	Ivacaftor given twice daily and dose according to patient weight: =>7 kg to <14 kg 50mg twice daily =>14kg to <25kg 75 mg twice daily =>25kg 150mg twice daily
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	• Reduced treatment burden • Improved lung function • Improved health related quality of life • Reduced pulmonary exacerbations • Improved survival
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

7. Mepolizumab for the treatment of relapsed or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Application

7.1. The Advisory Committee reviewed the application for mepolizumab for the treatment of relapsed or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

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

Recommendation

7.3. The Advisory Committee **recommended** that access to mepolizumab be widened for the treatment of relapsed or refractory eosinophilic granulomatosis with polyangiitis with a **high priority** within the context of treatment of respiratory disease, subject to the following Special Authority criteria:

> **MEPOLIZUMAB**
> **Initial application – Relapsed or refractory eosinophilic granulomatosis with polyangiitis**
> Applications only from a respiratory physician, clinical immunologist, or rheumatologist.
> Approvals valid for 12 months for applications meeting the following criteria:
> **All of the following**
> 1. The patient has eosinophilic granulomatosis with polyangiitis; and
> 2. The patient has trialled and not received adequate benefit from at least one of the following: cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, or rituximab at maximum tolerated dose for at least three months (unless contraindicated to all); and
> 3. Either:
> 3.1 The patient has trialled prednisone for a minimum of three months and is unable to maintain disease control at doses below 7.5 mg per day; or
> 3.2 Corticosteroids are contraindicated.
>
> **MEPOLIZUMAB**
> **Renewal application – Relapsed or refractory eosinophilic granulomatosis with polyangiitis**
> Applications from any relevant specialist. Approvals valid for 12 months where patient has no evidence of clinical disease progression.

7.4. In making this decision, the Advisory Committee considered:

- The high health need for those with relapsed or refractory EGPA, particularly regarding the decreased quality of life and poor health outcomes experienced by individuals with this condition.

- The strong evidence of benefit of mepolizumab in sustaining remission, reducing oral corticosteroid dose, and improving symptom-related quality of life in those with relapsed or refractory EGPA compared to currently funded treatments.

Discussion

Māori impact

7.5. The Committee considered that evidence on the impact of EGPA in Māori was limited. However, it was considered that conditions presenting with similar symptoms to EGPA such as asthma show that hospitalisation rates for Māori were approximately 2.84 times higher than non-Māori/Pacific/Asian, and mortality rates were 4.26 times higher (Asthma Respiratory Foundation NZ. 2018). Additionally, the Committee noted that a New Zealand study on the incidence of Wegener's granulomatosis (WG) and WG-like disease (including EGPA) reported that the rate among Europeans was twice that of New Zealand Māori or Asians (O'Donnell et al. Intern Med J. 2007;37:242-6). The Committee also considered that the treatment of EGPA aligns with Pharmac's Hauora Arotahi (Māori health areas of focus), which includes romaha ora (respiratory health).

Discussion

7.6. The Committee noted that EGPA (also known as Churg-Strauss syndrome or allergic granulomatosis and angiitis) is a multisystem autoimmune disorder characterised by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis of one or more end-organs. It was noted that almost all patients (>90%) have a history of bronchial asthma, and the median duration from onset of asthma to diagnosis of EGPA

is 5-9 years (Futura et al. Allergology Int. 2019;68:430-6). The Committee also noted the most commonly involved organ is the lungs, followed by the skin, however EGPA can affect any organ system, including the cardiovascular, gastrointestinal, renal, and central nervous systems (Wechsler et al. N Engl J Med. 2017;376:1921-32; UpToDate. King. 2020).

7.7. The Committee noted that internationally the annual incidence and prevalence of EGPA is 0.9 to 2.4 per million and 10.7 to 17.8 per million, respectively (Furuta et al. Allergology International. 2019;68:430-6). The Committee considered that the applicant's EGPA incidence estimate of approximately 1-2 patients per year and prevalence estimate of 50-90 patients in New Zealand was accurate. The Committee noted that 15% of EGPA patients are estimated to have relapsed or be refractory to current treatment, and 60% of EGPA patients are ANCA-negative (Pagnoux et al. Expert Rev Clin Immunol. 2016;12:1059-67; Ullah et al. Respir Med Case Rep. 2019;27:100830).

7.8. The Committee noted that those with EGPA may experience an array of symptoms depending on the phase of their disease state and the organs involved, with a major complaint among EGPA patients being dyspnoea and cough (Sokołowska et al. Clin Rheumatol. 2013;32:779-85). The Committee considered that those experiencing relapses are exposed to risk of end organ damage. The Committee considered that the health-related quality of life in people with EGPA is lower than that of those without EGPA, even when in remission. The Committee considered that those with EGPA have reduced overall survival when compared to those without EGPA, with a 5-year mortality rate of 10-15% (Tsurikisawa et al. J Rheumatol. 2017;44:1206-15; Saku et al. J Rheumatol. 2018;45:1159-66; Samson et al. J Autoimmun. 2013;43:60-9; Moosig et al. Ann Rheum Dis. 2013;72:1011-7). Additionally, the Committee considered those with EGPA may experience treatment burden due to the potential side effects of existing treatments.

7.9. The Committee considered that there is a significant carer burden for the whānau and family of those with EGPA. The Committee noted that both patients and carers face a range of challenges in the management of EGPA, including the physical and psychological impacts of the disease, the need for constant vigilance, and fear of the future (Mooney et al. Rheumatol Adv Pract. 2019;1:1).

7.10. The Committee considered that systemic corticosteroids are the first-line treatment for EGPA, however that long-term use introduces the risk of adverse effects and physiological dependence, with some individuals experiencing frequent relapses during corticosteroid tapering. It was considered that cyclophosphamide is used in relapsed disease where vasculitic symptoms are uncontrolled or large doses of corticosteroids are required. The Committee considered that second-line immunosuppressants for relapsed/refractory EGPA include azathioprine, cyclosporine, leflunomide, methotrexate, mycophenolate (all currently funded with no Special Authority restrictions), and rituximab (funded under Special Authority criteria for ANCA-associated vasculitis). The Committee considered that use of these agents also raises concern for long-term side effects.

7.11. The Committee considered that those patients living in rural areas and those requiring treatments that are administered in a hospital or outpatient setting (eg rituximab) may be disproportionately impacted by EGPA, as they are more likely to experience difficulty in accessing services including specialist visits and supportive care. The Committee also considered that, when assessing the impact of asthma, there is a clear socio-economic gradient in asthma hospitalisation, with the most socioeconomically

deprived areas having a hospitalisation rate 2.70 times that of the wealthiest areas, and a mortality rate 2.16 times higher (Asthma Respiratory Foundation NZ. 2018).

7.12. The Committee noted that the treatment of EGPA aligns with the Government's strategic priority to improve health outcomes for New Zealanders with long-term conditions, which includes chronic respiratory disease. Given the patient number estimates for this population group, it was also noted that relapsed/refractory EGPA falls under Pharmac's definition of a rare disorder, which is also a specific Government priority condition.

7.13. The Committee noted that mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which inhibits the bioactivity of IL-5, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils. The Committee noted that mepolizumab is Medsafe approved for relapsed or refractory EGPA in adult patients aged 18 years and over, and that the recommended dose for this indication is 300 mg once every 4 weeks administered via subcutaneous injection (Medsafe datasheet: Nucala 2020). The Committee considered that there is also evidence from real life observational studies (including a multicentre European cohort of 203 patients) indicating that 100 mg mepolizumab every 4 weeks is also effective for the treatment of EGPA (Bettiol et al. Arthritis Rheumatol. 2022;74:295-306) .

7.14. The Committee noted that the key evidence for mepolizumab for the treatment of relapsed or refractory EGPA comes from three clinical studies:

7.14.1. The Committee noted that NCT02020889 was a phase III, randomised, double-blind, parallel-group, multicentre trial that compared the efficacy of 300 mg mepolizumab once every 4 weeks via subcutaneous injection to placebo in 136 adult patients with relapsing or refractory EGPA. The Committee noted that after 52 weeks, the mepolizumab treatment led to ≥24 accrued weeks of remission in 28% of participants versus 3% in the placebo group (odds ratio [OR], 5.91; 95% confidence interval [CI], 2.68 to 13.03; *P*<0.001). The Committee also noted that mepolizumab treatment led to 32% of participants in remission at both week 36 and week 48, versus only 3% in the placebo group (OR, 16.74; 95% CI, 3.61 to 77.56; *P*<0.001). The Committee noted that the proportion of participants experiencing adverse events (AEs) in mepolizumab- and placebo-groups were 97% and 94%, respectively, with the most common AEs being headache (32% vs. 18%), arthralgia (22% vs. 18%), sinusitis (21% vs. 16%), and upper respiratory tract infection (21% vs. 16%) (Wechsler et al. N Engl J Med. 2017;376:1921-32).

7.14.2. The Committee noted that another publication also reporting on the NCT02020889 trial investigated the proportion of patients experiencing any clinical benefit; a composite endpoint defined as patients who had achieved remission, a 50% or greater reduction in oral corticosteroid dose during weeks 48 to 52, or no relapsed of EGPA during the 52-week study period. The Committee noted that participants experiencing any clinical benefit ranged from 78% to 87% in mepolizumab group versus 32% to 53% in the placebo group. The Committee noted that significantly more patients experienced clinical benefit with mepolizumab versus placebo in the blood eosinophil count less than 150 cells/mL subgroup (72% vs. 43%, *P*=0.033) and weight greater than 85 kg subgroup (68% vs. 23%, *P*=0.005) (Steinfeld et al. J Allergy Clin Immunol. 2019;143:2170-7).

7.14.3. The Committee noted that NCT00716651 was an extended follow-up of a phase II, single centre open label, prospective trial which investigated the efficacy of 750 mg mepolizumab every 4 weeks via intravenous infusion followed by methotrexate 0.3 mg/kg maintenance on remission in nine adult patients with relapsing or refractory

EGPA. The Committee noted that after a median follow up of 22 months (range 7 to 30 months), three out of the nine patients remained in remission. The Committee noted that, overall, five major relapses in three and seven minor relapses in five out of the total nine patients were recognised. It was also noted that the mean eosinophil counts rose after stopping the anti-IL-5 medication, and in six of the nine patients, corticosteroid doses had to be increased above 7.5 mg/d (Herrmann et al. Clin Exp Rheumatol. 2012;30:S62-5).

7.14.4. The Committee noted that GRANT00375947 was an open-label pilot safety study (as a dose-tapering case series) which investigated the efficacy of 750 mg mepolizumab once a month for 4 months via intravenous infusion, followed by a washout and safety-monitoring phase, in seven adult patients with EGPA. The Committee noted that after the 44-week study period, the primary outcome of the mean lowest daily prednisone dose achieved at the end of the treatment phase was 4.6 mg, a 64% reduction (*P*=0.0001) from the mean daily baseline dose of 12.9 mg. The Committee noted that the exacerbation rate during the treatment period was 0.14 (2 events during a 14-week period) compared to 0.69 during the non-treatment period (18 events over a 26-week period). (Kim et al. J Allergy Clin Immunol. 2010;125:1336-43).

7.15. The Committee considered that the evidence indicated that mepolizumab is effective in sustaining remission in those with relapsed or refractory EGPA, thereby improving symptom-related quality of life, reducing maintenance corticosteroid dosing, decreasing risk of end organ damage, and decreasing mortality. The Committee considered that the side effect profile was also reported to be more favourable for mepolizumab than currently funded immunosuppressants. The Committee considered that mepolizumab may also provide a health benefit for whānau and family via reduced carer burden and increased participation in society for patients in remission. It was also noted that there are early-stage clinical trials investigating the use of pembrolizumab in EGPA, which may be a future treatment option in this space.

7.16. The Committee considered that, if access to mepolizumab were to be widened, both ANCA-positive and ANCA-negative patients with relapsed or refractory EGPA should be eligible for funding under the Special Authority criteria, given the significant health need and clear health benefit in both groups. The Committee considered that there is no evidence to suggest that mepolizumab would be less effective in those who have not responded to cyclophosphamide versus those who are contraindicated to cyclophosphamide. The Committee also considered that the treating specialist is likely to vary depending on the phase of illness, with respiratory physicians predominantly managing the prodromal and secondary phase and rheumatologists or immunologists becoming involved in the vasculitic phase. The Committee noted that the eosinophil count does not necessarily correlate to disease activity, and therefore considered eosinophil counts would not offer effective targeting of people with severe disease if included within the funding restrictions.

7.17. The Committee considered that if access to mepolizumab were to be widened to patients with relapsed or refractory EGPA, it would likely be used in combination with a reduced dose of prednisone. The Committee considered that mepolizumab would also be expected to replace use of second line immunosuppressants in most of those who meet the proposed Special Authority criteria, but that some individuals may need to continue this treatment.

7.18. The Committee noted that mepolizumab is formulated as a solution for or powder for subcutaneous injection, allowing administration in the community setting. It was noted that this would reduce the impact on hospital staff, however, depending on where this medication is administered, may place a potential burden on patients and/or caregivers

who must travel from rural or remote areas to receive treatment. The Committee considered that those willing to self-administer mepolizumab would initially require training, however that this is not likely to vary significantly from what is required for individuals receiving treatment under current Special Authority criteria. The Committee considered that the once-monthly dosing of mepolizumab would also provide a suitability benefit over other currently funded treatments.

7.19. The Committee considered that the additional cost of widening of access to mepolizumab to patents with relapsed or refractory EGPA is likely to be minimal. The Committee considered widening access is also expected to lessen the impact on the health sector through reduced exacerbations, hospital visits, and effects of long-term oral corticosteroid use. The Committee considered health-sector resource costs for a person with EGPA in remission is likely to be significantly less than that of a person with relapsed EGPA. The Committee considered that initial uptake of mepolizumab is expected to be high (approximately <15 patients), as those with relapsed or refractory EGPA will have likely already trialled multiple alternative medications with a poor prognosis. The Committee also considered that those with an eosinophil count of >0.5 $\times 10^9$ cells/L are likely to already be eligible for funded treatment under current Special Authority criteria, although that patient numbers for this cohort is uncertain.

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

Population	People with relapsed or refractory EGPA • Unable to reduce prednisone dose below 7.5 mg daily or unable to tolerate corticosteroids • Patient has trialled and not received adequate benefit from at least one of the following: cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, or rituximab
Intervention	Mepolizumab 300 mg via SC injection once every 4 weeks with continued prednisone of up to 7.5 mg daily
Comparator(s) (NZ context)	BSC: • Prednisone >7.5 mg daily • Cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, or rituximab
Outcome(s)	Higher rates of clinical remission Reduced prednisone dose Reduction in long term corticosteroid usage Evidence extrapolated to assume: - Reduction in specialist costs and inpatient admissions - Improved health related quality of life (magnitude uncertain given the lack of quality-of-life data in EGPA) - Improved overall survival
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).	

Comparator: 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).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

8. Adrenaline auto-injector for the emergency treatment of anaphylaxis in the community

Application

8.1. The Committee reviewed the application for adrenaline auto-injector for the first aid treatment of anaphylaxis.

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 adrenaline auto-injector be listed with a high priority within the context of treatments for respiratory disease and allergies, subject to the following Special Authority criteria:

> **Special Authority for subsidy**
> Initial – (anaphylaxis) application from any Relevant Practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Both:
> 1. Either:
> 1.1 Patient has experienced a previous anaphylactic reaction which has resulted in presentation to a hospital or emergency department; or
> 1.2 Patient has been assessed to be at significant risk of anaphylaxis by, or on the recommendation of a relevant specialist; and
> 2 Patient is not to be prescribed more than two devices in initial prescription.
>
> Note: a limit of two devices applies to the initial prescription. Additional prescriptions are limited to repeat prescriptions of up to two devices prior to expiry unless device is being prescribed as a replacement for a device used in the treatment of anaphylaxis.

8.4. The Committee considered the unmet health need of people who experience anaphylaxis, the benefit of this medicine in the emergency treatment of anaphylaxis in the community and the suitability compared to currently funded treatments.

Discussion

8.5. The Committee noted Pharmac had received an application to fund an adrenaline auto-injector product in 1997 and had received clinical advice from Pharmacology and Therapeutics Advisory Committee (PTAC) as summarised on the Application Tracker.

8.6. The Committee noted it had requested at its meeting in October 2020 to see Pharmac's assessment of the adrenaline auto-injector.

8.7. The Committee noted anaphylaxis is a severe, potentially life-threatening allergic reaction and that adrenaline auto-injectors are the recommended emergency first-aid treatment for anaphylaxis.

8.8. The Committee noted historically the reported estimated mortality from anaphylaxis in New Zealand was calculable to approximately 2.7 deaths per 100,000 per year (with a range of 0.6 to 10.6) (Pumphrey RS. Clin Exp Allergy. 2000;30:1144-50; Low &

Stables. Pathology. 2006;38:328-3). The Committee noted about 20 – 33% of deaths occurred in people who had previously experienced a severe allergic reaction and that a further 50% of people have had a previous mild or moderate reaction (Pumphrey 2000; Low & Stables 2006; Macdougall et al. Arch Dis Child. 2002;86:236-9; Bock et al. J Allergy Clin Immunol. 2001;107:191-3; Sampson et al. N Engl J Med 1992;327:380-4). Based on this evidence, the Committee considered not all people experiencing a life-threatening anaphylaxis reaction would have had a prior life-threatening reaction. The Committee considered atopy, particularly asthma, were important risk factors for anaphylaxis-associated fatality.

8.9. The Committee noted fatal food anaphylaxis most commonly occurs during the second and third decades of life and that delayed adrenaline administration is a risk factor. The Committee noted the risk factors for fatal venom anaphylaxis include middle age, male sex, white race and cardiovascular disease (Turner et al. JACIP. 2017;5:1169-78). The Committee noted however the overall absolute risk of a fatal event is very low.

8.10. The Committee noted the paediatric hospitalisation rates as reported by Gold et al, with a 15% hospitalisation rate post anaphylaxis if an auto injector was used, and 47% if not (Gold et al. J Allergy Clin Immunol. 2000;106:171-6). The Committee considered that the management of anaphylaxis has changed since this study was conducted. The Committee noted Yocum et al reported a 7% hospitalisation rate in untreated adults (Yocum et al. J Allergy Clin Immunol. 1999;104:452-6) and that both Yocum et al and Sorensen et al reported that 70 people per 4.4 million were hospitalised per annum (Sorensen et al. Allergy. 1989;44:288-90).

8.11. The Committee considered that while children had a higher rate of allergy, there was less risk of fatality in this age group and therefore the results of study from paediatric focussed studies could not be extrapolated to the wider population. The Committee noted that people who suffer an allergic reaction and receive adrenaline via an auto-injector often go to hospital for observation, based on the Australasian Society of Clinical Immunology and Allergy Guidelines 2021. Given admission in New Zealand is defined as more than three hours, the Committee considered a reduced admission rate may not be seen if adrenaline auto-injector were to be funded as these patients would continue to be monitored in hospital for four hours. The Committee considered that the majority of patients are likely to be treated in the Emergency Department, with only severe cases admitted overnight.

8.12. The Committee considered there was no evidence or data to suggest anaphylaxis disproportionately affects Māori or Pacific peoples but that the lack of public allergy services in New Zealand likely contributed to inequitable management of anaphylaxis. The Committee also considered the lack of allergists across the country created inequities in access to care. The Committee considered first generation immigrants in New Zealand may have an increased risk of severe allergy.

8.13. The Committee noted Pharmac currently funds adrenaline in glass ampoules from which the correct volume of adrenaline injected needs to be drawn up into a syringe and fitted with an appropriate needle for administration, a process requiring a number of steps which could be problematic, particularly in a pressured situation. The Committee noted that vial or ampoule presentations that require the adrenaline to be drawn up at the time of use are not recommended in clinical guidelines. The Committee considered the presence of adrenaline in glass ampoules within guidelines was unlikely to change given the lack of evidence. The Committee considered that these ampoules are not suitable for use in the community, therefore the appropriate

comparator for assessment of the benefit of an adrenaline auto injector should be placebo.

8.14. The Committee noted that to gain benefit, patients must have the auto-injector to hand and use it correctly. The correct usage of auto-injectors occurs in about 50% of cases and a repeat dose may be needed (Armstrong et al. Health Technol Assess. 2013;17:1-117, v-vi). The Committee considered that correct usage rates would be expected to be higher now, and that with training, these would be expected to increase to approximately 90%. The Committee noted that people who have adrenaline administered correctly would be expected to receive an 83% reduction in mortality rates (Pumphrey 2000) and a reduced hospitalisation of 34% (Gold et al. 2000) which would be expected to reduce the average duration of hospitalisation.

8.15. The Committee noted that people are more likely to access an adrenaline auto-injector if they have previously experienced an anaphylactic reaction. The Committee noted that Pharmac's assessment included people who had not previously had an anaphylaxis, and that these patients would not gain as significant benefit from an auto-injector as those who have previously experienced a previous reaction. The Committee considered any patient who had experienced an anaphylactic reaction would gain benefit from an adrenaline auto-injector.

8.16. The Committee considered that the impact on health-related quality of life was an important consideration in the assessment of adrenaline auto-injectors. The Committee considered that the NICE assessment relating to the quality of life associated with anaphylaxis (in the absence of an adrenaline autoinjector) and the quality-of-life improvement associated with adrenaline auto-injector would be an appropriate consideration for this patient group. The Committee noted that 40-50% of patients with an episode of anaphylaxis experience post-traumatic stress disorder (PTSD) and 70-75% experience anxiety or depression (Lee et al. Allergy Asthma Immunol Res. 2020;12:496-506). The Committee also considered parent's and caregivers' health-related quality of life can be significantly affected. The Committee noted studies have reported that the health-related quality of life rated by people who are at risk of anaphylaxis is lower than that of people with type 1 diabetes mellitus and rheumatic heart disease (Lange L. Allergo J Int. 2014; 23:252-60, Manassis K. J Allergy (Cairo). 2012;2012:316296). The Committee noted evidence that having an auto-injector can reduce health-related quality of life and considered this may be related to a fear of using the device. The Committee noted evidence to support a reduction in anxiety in 64-70% of parents and caregivers (Allen et al. J Paediatr Child Health. 2015;51:696-8.) although that same study reported 90% of children had no change in anxiety.

8.17. The Committee considered the evidence relating to the health benefits from adrenaline auto-injectors to be of moderate strength and weak quality. However, given adrenaline auto-injectors were included in the majority of guidelines, the Committee considered no further data would become available as it would be unethical to run a randomised control trial in which a group of people were not provided with an auto-injector.

8.18. The Committee considered it appropriate to use available Australian data to inform patient number and uptake estimates. The Committee considered Pharmac's assessment regarding the likely patient population and use of adrenaline auto-injectors was reasonable. The Committee highlighted that currently, if a person has self-funded an adrenaline auto-injector and then uses it, ACC will pay for the cost of a replacement. The Committee considered the current funding results in inequities.

8.19. The Committee noted that there is a scarcity of specialist allergy services in New Zealand. The Committee considered that training in correct use of the adrenaline autoinjector would have a significant impact on sector resource and that resource to support training and education may not be available currently. However, the Committee considered that such training would significantly improve the confidence and use of auto-injectors among caregivers and patients. The Committee considered it important that all patients have an appropriate action plan (eg from the Australasian Society of Clinical Immunology and Allergy).

8.20. The Committee considered there are people in rural communities at high risk of anaphylaxis who would be seen in general practice. The Committee considered that the funding restrictions would need to reflect the diverse range of clinicians likely to support people at high risk of anaphylaxis.

8.21. Overall, the Committee considered there would be benefit from funding adrenaline auto-injectors, given the primary reason for anaphylaxis-related mortality is lack of adrenaline, alongside lessened anxiety-related quality of life impacts. However, the Committee considered the true benefit was hard to quantify and that it was unlikely any further evidence would become available, noting adrenaline auto-injectors are funded in the majority of similar jurisdictions. The Committee considered that it would be important to obtain feedback on the posed special authority criteria from the Allergy Society of New Zealand and Australasian Society of Clinical Immunology and Allergy.

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

Population	• Patients who have had an anaphylactic reaction • Patients identified at significant risk of a severe anaphylactic reaction
Intervention	Adrenaline auto-injector, at least one injection of 0.15 mg or 0.3 mg (weight dependent)
Comparator(s)	Placebo - emergency hospital treatment following event
Outcome(s)	• Reduction in hospitalisations (noting all patients should be monitored in hospital following adrenaline administration) • Minimal improved anaphylactic-related mortality • Reduction in anxiety-related quality-of-life impact
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.	

9. Nintedanib (Ofev) and pirfenidone for expanded range of progressive fibrosing interstitial lung diseases (PFILDs)

Application

9.1. The Committee reviewed the clinician application for nintedanib for progressive fibrosing interstitial lung diseases (PFILDs).

9.2. The Committee noted that Pharmac staff also sought advice regarding pirfenidone for the same patient populations.

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 access to nintedanib be widened to include patients with PFILDs with a **high priority** within the context of treatment of respiratory disease, subject to the following Special Authority criteria (additions shown **in bold**):

> NINTEDANIB
> Initial application — (idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease)** only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease** by a multidisciplinary team including a radiologist; and
> 2. Forced vital capacity is between 50% and 90% predicted; and
> 3. Nintedanib is to be discontinued at disease progression (See Note); and
> 4. Nintedanib is not to be used in combination with subsidised pirfenidone; and
> 5. Any of the following:
>   - 5.1 The patient has not previously received treatment with pirfenidone; or
>   - 5.2 Patient has previously received pirfenidone, but discontinued pirfenidone within 12 weeks due to intolerance; or
>   - 5.3 Patient has previously received pirfenidone, but the patient's disease has not progressed **(See Note)** ~~disease progression defined as 10% or more decline in predicted FVC within any 12 month period~~ since starting treatment with pirfenidone.
>
> Renewal — (idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease)** only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Treatment remains clinically appropriate and patient is benefitting from and tolerating treatment; and
> 2. Nintedanib is not to be used in combination with subsidised pirfenidone; and
> 3. Nintedanib is to be discontinued at disease progression (See Note).
>
> Note: Disease progression is defined as a decline in percent predicted FVC of 10% or more within any 12 month period.

9.5. The Committee **recommended** that access to pirfenidone be widened to include patients with PFILDs with a **medium priority** within the context of treatment of respiratory disease, subject to the following Special Authority criteria (additions shown **in bold**):

> PIRFENIDONE
> Initial application — (idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease)** only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:

1. Patient has been diagnosed with idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease** by a multidisciplinary team including a radiologist; and
2. Forced vital capacity is between 50% and 90% predicted; and
3. Pirfenidone is to be discontinued at disease progression (See Note); and
4. Pirfenidone is not to be used in combination with subsidised nintedanib; and
5. Any of the following:
    5.1 The patient has not previously received treatment with nintedanib; or
    5.2 Patient has previously received nintedanib, but discontinued nintedanib within 12 weeks due to intolerance; or
    5.3 Patient has previously received nintedanib, but the patient's disease has not progressed **(See Note)** ~~disease progression defined as 10% or more decline in predicted FVC within any 12 month period~~ since starting treatment with nintedanib.

Renewal — (idiopathic pulmonary fibrosis **or progressive fibrosing interstitial lung disease)** only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Treatment remains clinically appropriate and patient is benefitting from and tolerating treatment; and
2. Pirfenidone is not to be used in combination with subsidised nintedanib; and
3. Pirfenidone is to be discontinued at disease progression (See Note).

Note: Disease progression is defined as a decline in percent predicted FVC of 10% or more within any 12 month period.

9.6. The Committee **recommended** that, if nintedanib were funded for PFILDs, that access to pirfenidone be widened to include the subgroup of patients with PFILDs for whom nintedanib is not tolerated with a **high priority** within the context of treatment of respiratory disease, subject to the following Special Authority criteria:

PIRFENIDONE
Initial application — (idiopathic pulmonary fibrosis or progressive fibrosing interstitial lung disease) only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Either
    1.1. Both:
        1.1.1. Patient has been diagnosed with idiopathic pulmonary fibrosis by a multidisciplinary team including a radiologist; and
        1.1.2. Any of the following:
            1.1.2.1. The patient has not previously received treatment with nintedanib; or
            1.1.2.2. Patient has previously received nintedanib, but discontinued nintedanib within 12 weeks due to intolerance; or
            1.1.2.3. Patient has previously received nintedanib, but the patient's disease has not progressed **(See Note)** ~~disease progression defined as 10% or more decline in predicted FVC within any 12 month period~~ since starting treatment with nintedanib.
    1.2. Both:
        1.2.1. Patient has been diagnosed with progressive fibrosing interstitial lung disease by a multidisciplinary team including a radiologist; and
        1.2.2. Patient has previously received nintedanib, but discontinued nintedanib within 12 weeks due to intolerance; or
2. Forced vital capacity is between 50% and 90% predicted; and
3. Pirfenidone is to be discontinued at disease progression (See Note); and
4. Pirfenidone is not to be used in combination with subsidised nintedanib.

Renewal — (idiopathic pulmonary fibrosis or progressive fibrosing interstitial lung disease) only from a respiratory specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Treatment remains clinically appropriate and patient is benefitting from and tolerating treatment; and
2. Pirfenidone is not to be used in combination with subsidised nintedanib; and
3. Pirfenidone is to be discontinued at disease progression (See Note).

Note: Disease progression is defined as a decline in percent predicted FVC of 10% or more within any 12 month period.

9.7. In making its recommendations, the Committee considered:

- The high health needs of people with PFILDs and their families/whanau who are impacted by this progressive and debilitating disease, in which the decline in lung function indicated by reduced forced vital capacity (FVC) is associated with a lack of independent functioning and with premature death

- That respiratory disease is one of Pharmac's Māori health areas of focus and that Māori who have respiratory disease often present later in the disease course than non-Māori

- That the evidence base for nintedanib was stronger and of higher quality than the evidence base for pirfenidone, although it was reasonable to assume that pirfenidone would provide a reduction in lung function decline similar to that from nintedanib despite this not being demonstrated in the published clinical trials

- That a reduction in the rate of annual FVC decline in PFILDs with nintedanib or pirfenidone would be expected to translate into a reduction in exacerbations and/or a mortality benefit, and that these medicines would be significant for PFILDs given the dismal nature of the disease

- The benefits of harmonising the funded pharmaceutical treatment of PFILDs with the funded pharmaceutical treatment of IPF.

Discussion

Māori impact

9.8. The Committee noted that there is limited data on the impact of PFILDs for Māori, however, some underlying connective tissue disease-associated ILDs are more common in Māori than in non-Māori. The Committee noted that respiratory disease is known to have an inequitable impact on Māori, that Māori who have respiratory disease often present later than non-Māori with respiratory disease, and that respiratory disease is one of Pharmac's Hauora Arotahi (Māori health areas of focus).

Discussion

9.9. The Committee noted that interstitial lung disease (ILD) describes a heterogenous group of disorders characterised by progressive inflammation and fibrosis of the lung tissue. The Committee noted that a subset of patients 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 of PFILD. The Committee noted that diagnosis is multidisciplinary and that certain diagnostic features are consistently present in PFILDs (ie increasing fibrosis, decline in forced vital capacity [FVC] ≥10% and gas exchange, worsening of symptoms and exercise capacity, and deterioration in lung function). The Committee noted that idiopathic pulmonary fibrosis (IPF) is one of the most common

types of ILD and that other types of chronic fibrosing ILD may develop a progressive phenotype. The Committee noted that PFILDs are associated with poor response to treatment and disease progression despite treatment (Cottin et al. Eur Respir Rev. 2018;27:180076; Wong et al. Respir Res. 2020;21:32; George et al. Lancet Respir Med. 2020;8:925-34).

9.10. The Committee noted that nintedanib and pirfenidone are each funded in New Zealand with identical restrictions to IPF with FVC between 50% and 90% predicted. The Committee noted that nintedanib and pirfenidone are not subsidised in combination with each other and patients can only switch between these treatments if the patient is intolerant of, or has not progressed on, treatment with the other agent.

9.11. The Committee noted that the applicant proposed access to nintedanib be widened to include the treatment of patients with PFILDs that have not stabilised with immunomodulatory therapy alone (such as those with connective tissue disease-associated ILD, interstitial pneumonia with autoimmune features, stage four sarcoidosis, chronic hypersensitivity pneumonia, pleuroparenchymal fibrosing elastosis) or for whom such treatment is proven ineffective (such as asbestosis). The Committee noted that the applicant provided a position statement from the Thoracic Society of Australia and New Zealand (TSANZ) (Jee et al. Respirology. 2021;26:23-51). The Committee agreed with the population described by the applicant as having PFILDs, however, considered that using a list of specific clinical definitions would be too restrictive to effectively target funding given there are about 70 types of PFILD.

9.12. The Committee noted that the population with PFILDs is heterogeneous and that prevalence data for PFILDs as a group is scarce. The Committee noted that registry data suggests prevalence of around 5 per 100,000 in the New Zealand population and based on this, approximately 260 prevalent patients would exist. The Committee considered this estimate was uncertain but that it was likely reasonable based on clinical experience.

9.13. The Committee noted that there is limited data on the impact of PFILDs for Māori, however, was made aware of evidence that the some of the underlying connective tissue diseases associated with ILDs such as systemic lupus erythematosus (SLE) are more common in Māori than in non-Māori (McDougall et al. Semin Arthritis Rheum. 2017;46:675-86). The Committee noted that respiratory disease is known to have an inequitable impact on Māori, that Māori who have respiratory disease often present later than non-Māori with respiratory disease, and that respiratory disease is one of Pharmac's Hauora Arotahi (Māori health areas of focus).

9.14. The Committee noted that treatment of PFILDs depends on the underlying disease, and the choice of treatment (eg immunosuppressant) can vary around the country. The Committee considered that the current funding of nintedanib and pirfenidone for the treatment of IPF until progression results in a population of patients experiencing good therapeutic effect who receive long-term treatment. The Committee noted that approximately 20% of patients do not tolerate nintedanib. The Committee considered that similar to IPF, the unmet need in PFILDs is due to the decline in lung function leading to mortality and morbidity despite available treatments. The Committee therefore considered that clinicians would want to treat PFILDs promptly, given the progressive nature of the disease. The Committee considered that the comparator would be best supportive care for most patients, not lung transplant or specific medicines. The Committee considered that transplantation is only performed for a small number of patients with PFILDs, as most patients are of older age, are less likely to be suitable for transplant at presentation and would be expected to have poor outcomes in comparison with other settings.

9.15. The Committee considered that the evidence for health needs in PFILDs is of moderate strength and low to moderate quality, and predominantly comes from the placebo arms of clinical trials due to the heterogenous causes of this disease and corresponding scarcity of descriptive epidemiological data. The Committee considered that although there is a lack of data on PFILDs as a group, there is evidence of the health needs of individuals with underlying conditions (eg rheumatological diseases). The Committee was made aware of evidence of a similar FVC decline over one year in patients with IPF compared with patients with fibrosing lung disease (Brown et al. Eur Respir J. 2021;58:2100221). The Committee was also made aware of evidence from a two-year retrospective observational UK study that included about 15% of patients who fulfilled eligibility criteria for the INBUILD trial of nintedanib for PFILD (key evidence for this application described later in this record) despite being on standard treatments, and noted its authors reported a similar probability of death over time with IPF and PFILD (Simpson et al. Eur Respir J. 2021;58:2100221). The Committee considered that the 15% of patients with a progressive phenotype could not be identified prospectively. The Committee considered that the health need of people with PFILDs is similar to that of people with IPF, where comorbidities affect the underlying disease and the decline in FVC is associated with a lack of independent functioning and with premature death. The Committee considered that a reduction in the rate of annual FVC decline in PFILDs would be expected to translate into a reduction in exacerbations and/or a mortality benefit.

9.16. The Committee considered that the health needs of family/whānau of people with PFILDs are similar to that of family/whānau of people with IPF or other types of premature respiratory failure, where there is a significant impact on family/whānau with support needs increasing as the patient's lung function declines and the disease has a greater effect.

9.17. The Committee noted that nintedanib has been recommended for funding for the treatment of patients with PFILDs with FEV ≥45% of predicted in Australia (PBAC, 2021) and in Canada (CADTH-CDEC, 2021); for patients with chronic fibrosing ILDs with a progressive phenotype other than IPF in Scotland (SMC, 2021); and for chronic fibrosing ILDs with a progressive phenotype in England and Wales (NICE, 2021). The Committee noted the NICE assessment included a company estimate of nearly 900 patients in the UK with PFILD and that nintedanib would be used as an additive treatment rather than replacing other therapies. The Committee noted that no specific recommendations regarding the funding of pirfenidone for PFILDs were identified from these international funding agencies.

Nintedanib evidence

9.18. The Committee noted that the key evidence for nintedanib in PFILDs comes from the INBUILD trial, a randomised (1:1), double-blind, placebo-controlled, phase III, multicentre, 52-week study of oral nintedanib 150 mg twice daily vs placebo in 663 patients with fibrosing lung disease affecting >10% of lung volume on high-resolution CT (Flaherty et al. N Engl J Med. 2019; 381:1718-27). The Committee noted that INBUILD patients had progression of ILD in the past 24 months despite treatment (defined as a decline in FVC >10% OR 5<10% + worsening symptoms or fibrosis on CT scan), FVC ≥45% of predicted value, and diffusing capacity of the lung for carbon monoxide (DLCO) 30%-<80% of predicted value. The Committee noted that other treatments were not permitted at study entry except for low dose prednisone, although other treatments could be started after six months and this occurred in about 20% of patients receiving placebo and about 10% of patients receiving nintedanib (Table S5, Supplementary Appendix). The Committee noted that 412 (62.1%) had a usual interstitial pneumonia (UIP)-like fibrotic pattern.

9.18.1. The Committee noted that the primary endpoint of INBUILD was the adjusted annual rate of decline in FVC, which was −80.8 ml per year with nintedanib vs −187.8 ml per year with placebo in the overall population (between-group difference, 107.0 ml; 95% confidence interval [CI], 65.4 to 148.5; P<0.001). The Committee noted that this difference was similar to that reported in the INPULSIS trials of nintedanib for IPF, which were reviewed by PTAC in August 2016. The Committee noted that the adjusted rate of decline in FVC in INBUILD for those with a UIP-like fibrotic pattern was −82.9 ml per year with nintedanib vs −211.1 ml per year with placebo (between-group difference, 128.2 ml; 95% CI, 70.8 to 185.6; P<0.001).

9.18.2. The Committee noted that after the last INBUILD patient had reached 12 months follow-up, the proportions of patients who had died or had an acute exacerbation were 12.3% nintedanib vs 17.8%+ placebo (HR 0.68, 95% CI 0.46 to 1.01), and the proportions of patients who had died were 8.1% nintedanib vs 11.5% placebo (HR 0.70, 95% CI 0.43 to 1.15). The Committee considered that the study was not powered for these outcomes, but nonetheless these results' central estimates suggested trends towards reductions in events with nintedanib that were clinically significant if not formally statistically significant.

9.18.3. The Committee noted that the most frequent adverse event (AE) in INBUILD was diarrhoea, which was reported in 222 (66.9%) nintedanib patients vs 79 (23.9%) placebo, and that abnormal liver function tests (≥3 times the upper limit of normal) were reported in 13.0% nintedanib vs 1.8% placebo. The Committee noted that AEs led to discontinuation in 19.6% nintedanib vs 10.3% placebo and led to dose reduction in 33.1% nintedanib vs 4.2% placebo. The Committee noted that nintedanib is not immunosuppressive, as many other treatments used for PFILDs are, and considered this an advantage.

9.18.4. The Committee noted a +0.55 point average absolute change in the total score on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire from baseline at week 52 (a secondary outcome of INBUILD) in the overall study population with nintedanib compared with −0.79 points with placebo (between-group difference 1.34 points; 95% CI, −0.31 to 2.98), and in patients with a UIP-like fibrotic pattern +0.75 points and −0.78 points respectively (between-group difference 1.53; 95% CI, −0.68 to 3.74). The Committee considered that the K-BILD questionnaire is not a widely used measure but that, while the results in this PFILD context indicated that there was no difference in quality of life (QOL) with nintedanib vs placebo, this was consistent with those results in IPF (where PTAC in August 2016 noted that the INPULSIS trials of nintedanib in IPF reported no statistically significant differences in changes in QOL (using the St George's Respiratory Questionnaire, SGRQ).

9.19. The Committee noted evidence from a pre-planned subgroup analysis of INBUILD according to ILD diagnosis, and considered this indicated that there was a consistent benefit in terms of reducing the rate of FVC decline across those subgroups (Wells et al. Lancet Respir Med. 2020;8:453-60).

9.20. The Committee noted evidence from the SENSCIS trial, a multicentre randomised (1:1), double-blind, placebo-controlled, parallel-group trial of 576 patients with ILD-associated systemic sclerosis, fibrosis affecting ≥10% of the lungs, FVC ≥40% of predicted value and DLCO 30-89% of the predicted value (Distler er al. N Engl J Med. 2019;380:2518-28). The Committee noted that patients received oral nintedanib 150 mg twice daily or placebo for 52 weeks and that patients receiving prednisone ≤10 mg per day, or receiving mycophenolate or methotrexate, were eligible. The Committee noted that not all SCENSIS patients would have met the criteria for progressive

disease used in routine practice (ie they did not have all diagnostic features consistently present in PFILDs).

9.20.1. The Committee noted that the primary endpoint of SENSCIS was the adjusted annual rate of decline in FVC, which was −52.4 mL/year with nintedanib vs −93.3 mL/year with placebo (difference, 41.0 mL/year; 95% CI: 2.9 to 79.0; P=0.04). The Committee noted that multiple-imputation sensitivity analyses for missing data yielded P values ranging from 0.06 to 0.10. The Committee noted that there was no difference in QOL between groups (using the SGRQ measure), and considered that tolerability was similar to that reported for INBUILD, noting an additional publication reporting safety and tolerability data from the SCENSIS trial (Seibold et al. Ann Rheum Dis. 2021;79:1478-84).

9.21. The Committee considered that there was moderate to high quality evidence, of moderate strength, for a reduced decline in lung function with nintedanib in PFILDs, similar to that seen with nintedanib in IPF. The Committee noted there was no difference in QOL with nintedanib, although the evidence was from short-term studies, and considered that a QOL benefit would be expected in a long-term study.

Pirfenidone evidence

9.22. The Committee noted evidence for pirfenidone in PFILDs from the prospective, randomised (1:1), placebo-controlled phase IIb RELIEF trial of oral pirfenidone (267 mg three times per day in week 1, 534 mg three times per day in week 2, and 801 mg three times per day thereafter) or matched placebo added to ongoing medication for a target of 374 patients with symptomatic PFILD (Behr et al. Lancet Respir Med. 2021;9:476-86). The Committee noted that eligible patients had an annual decline in predicted FVC of 5% despite conventional anti-inflammatory therapy, FVC 40-90%, and DLCO 25-75% (extended to 10-90%), and that patients with previous antifibrotic treatment were excluded.

9.22.1. The Committee noted that RELIEF was a 48-week study, however, after 127 patients had been randomised the study was prematurely terminated based on an interim analysis for futility triggered by slow recruitment. The Committee noted that the primary endpoint of RELIEF was the absolute change in percent predicted FVC from baseline to week 48, and noted that data missing for 60 patients (47%) had to be imputed using imputation methods that differed because of the premature trial termination. The Committee considered that the results of these analyses suggested a difference between pirfenidone and placebo, however, the number of evaluable patients was small and resulted in a large degree of uncertainty in the results.

9.23. The Committee noted evidence from a multicentre, international, double-blind, randomised (1:1), placebo-controlled phase II trial of 253 patients with progressive fibrosing unclassifiable interstitial lung disease (uILD) who received 2403 mg/day pirfenidone or placebo for 24 weeks (Maher et al. Lancet Respir Med. 2020;8:147-57). The Committee noted that participants had FVC decline >5% or significant symptomatic worsening, FVC ≥45%, >10% fibrosis on high-resolution CT, and DLCO ≥30%.

9.24. The Committee noted that the primary endpoint of the Maher et al. study was the mean change in FVC based on home spirometry over 24 weeks, however, analysis of the primary endpoint was affected by intra-individual variability in home spirometry values, which prevented application of the prespecified statistical model. The Committee noted that the predicted median change in FVC over 24 weeks measured using home spirometry was –87.7 (inter-quartile range: –338.1, 148.6) mL with

pirfenidone and –157.1 (–370.9, 70.1) mL with placebo, and considered there was a suggestion of a difference between groups. The Committee noted that the change in FVC based on site spirometry (a secondary outcome) between-treatment difference was 95.3 mL (95% CI: 35.9 to 154.6, P=0.002), and that patients were less likely to have a >5% decline in FVC with pirfenidone (odds ratio 0.42, 95% CI 0.25–0.69, P=0.001). The Committee considered this difference was similar to that with nintedanib in PFILDs.

9.25. The Committee noted that Maher et al. reported QOL (using SGRQ) was similar between groups. The Committee noted that the AEs with pirfenidone were slightly different to that occurring with nintedanib, that AEs occurring more frequently with pirfenidone than placebo were gastrointestinal events (47% vs 26%), photosensitivity (8% vs 2%) and weight loss (8% vs 1%), and that AEs led to treatment discontinuation in 19/127 (15.0%) pirfenidone and 5/124 (4.0%) placebo.

9.26. The Committee was made aware of TRAIL1, a double-blind, placebo controlled, randomised (1:1) controlled trial of 2403 mg/day pirfenidone or placebo for 52 weeks in patients wth rheumatoid arthritis associated-ILD with >10% fibrosis (FVC ≥40%, DLCO ≥30%). The Committee was made aware that the study recruited 123 of 270 planned patients, stopped early due to COVID-19, and the results (at https://www.medrxiv.org/content/10.1101/2022.04.01.22273270v1.full.pdf, pre-print webposting 1 April 2022) had not yet been peer-reviewed. The Committee was made aware that the composite primary outcome was ≥10% decline in FVC or death, reported in 11.1% pirfenidone vs 15% placebo (odds ratio 0.67; 95% CI 0.22 to 2.03), and that the reduction in FVC annual decline was –66mL pirfenidone vs –146mL placebo (P=0.008). Members considered that the rate of FVC decline as conveyed to them suggested a between-group difference of 80ml/year, although the meeting's appraisal of this evidence was limited.

9.27. The Committee considered that there was low quality evidence, of moderate strength, for pirfenidone being beneficial in PFILDs, noting the challenges encountered in the trials and therefore the uncertain immature evidence. However, the Committee considered that the evidence does suggest pirfenidone is effective in reducing FVC, which is biologically plausible. The Committee noted that the lack of a head-to-head trial with nintedanib means that it is unclear whether pirfenidone is similar or less effective than nintedanib. The Committee noted that AEs and dosing with pirfenidone were slightly different to that of nintedenib. The Committee considered that there was insufficient evidence from a subgroup analysis of the Maher et al. data (Kreuter et al. Adv Ther. 2022;39:1081-95) to suggest that risks or benefits would differ according to disease type, although the Committee considered that this is possible. The Committee considered that better data for pirfenidone may not eventuate, noting there are few new trials in this area recruiting or being published.

General

9.28. Overall, and noting the evidence of benefit with nintedanib in PFILDs, the Committee considered that it was reasonable to assume that pirfenidone would provide a reduction in lung function decline similar to that from nintedanib, despite this not being demonstrated in the published trials. The Committee considered that a reduction in the rate of annual FVC decline in PFILD with nintedanib or pirfenidone would be expected to translate into a reduction in exacerbations and/or a mortality benefit, and considered that these medicines would be significant for PFILDs given the dismal nature of the disease. The Committee considered that there remained some uncertainty whether all PFILD types would be expected to receive a similar magnitude of benefit from treatment with nintedanib or from pirfenidone, although the available evidence

suggests magnitude may be similar across PFILD types. The Committee considered there was evidence that PFILD patients receiving nintedanib would be expected to benefit similarly to the currently funded IPF patient group, and that the evidence suggested the same could be expected for PFILD patients receiving pirfenidone compared with IPF patients receiving pirfenidone. The Committee noted there was no evidence of an improvement in the QOL of family/whānau with nintedanib or pirfenidone, but considered that it was reasonable to assume there would be a QOL benefit for family/whānau due to the treated patient having a reduced requirement for care and support.

9.29. The Committee considered that, if nintedanib were funded for PFILDs, it would be beneficial to have funded access to pirfenidone for those patients with PFILDs for whom nintedanib is not tolerated given the high proportion of patients (19.6%) who discontinued treatment in the INBUILD trial. The Committee considered that this could improve the QOL of patients with PFILDs for whom nintedanib is not tolerated.

9.30. The Committee considered that the currently funded dose forms of pirfenidone (267 and 801 mg) were suitable and that the 534 mg tablets did not need to be funded, given the 534 mg dose is used for a week at most. The Committee considered that the pill size and dosage was not a significant issue relative to providing an effective treatment for this illness. The Committee considered that its appraisal of this application was not contingent on Medsafe approval of pirfenidone for the PFILD indication as there is extensive worldwide clinical experience with its use in PFILD. The Committee considered that the majority of patients with PFILDs would be commenced on nintedanib rather than pirfenidone, due to the greater evidence base for nintedanib.

9.31. The Committee considered that widening access to nintedanib and/or pirfenidone might displace other pharmaceutical treatments currently used for the treatment of PFILDs because some other treatments might be stopped early, although it would be expected that nintedanib or pirfenidone would be additional and that some other treatments would continue to be used. The Committee considered it was reasonable to assume this would occur in proportions of New Zealand patients similar to that in the clinical trial participants.

9.32. The Committee considered that the use of nintedanib and/or pirfenidone for PFILDs would be expected to reduce the frequency of exacerbations in people with PFILDs, with an approximate halving in exacerbations based on the INPULSIS and TOMORROW trials. Members also considered that the use of nintedanib and/or pirfenidone might avoid or delay the need for lung transplant, but that this would apply to only a very small number of patients, as most patients' disease would not be suitable for transplantation. Members however considered it would be important to include transplantation in any economic assessment, given the benefit nintedanib and/or pirfenidone would offer to those individuals and the wider health system. Members considered around one fifth of lung transplants were for ILDs.

9.33. The Committee considered that the health states and mortality assumptions used in the economic model by the NICE (England/Wales) in its assessment of nintedanib would be reasonable for Pharmac to use for cost-effectiveness estimates. The Committee considered that discontinuation rates would be similar for nintedanib and pirfenidone, as the clinical trial evidence reported similar absolute differences for each treatment vs placebo. The Committee considered that the lowest reported discontinuation rate would be most appropriate to model (either the discontinuation rate for IPF in New Zealand, or the INBUILD trial discontinuation rate of 19.6% as used by the PBAC).

9.34. The Committee considered that proposed changes to the Special Authority criteria to specifically include PFILDs (without further definition) would be appropriate, and noted that the current criteria stop treatment at progression and appropriately include a multidisciplinary team at diagnosis, which is important for PFILD given the consistent elements typically seen in PFILDs and the lack of consensus in definitions. The Committee considered that it would also be beneficial to harmonise the funded treatments for PFILDs with those for IPF given the overlap in these conditions, the benefits of treating progressing disease promptly, and the inability to prospectively identify the 15% of IPF patients whose disease will progress (based on Simpson et al. Eur Respir J. 2021).

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

Population	Patients diagnosed with PFILD with FVC between 50% and 90% predicted. Either no previous treatment with [nintedanib/pirfenidone] or received [nintedanib/pirfenidone] but discontinued within 12 weeks, or received [nintedanib/pirfenidone] previously but disease has not progressed.	
Intervention	Nintedanib: 150 mg nintedanib taken twice per day. Initial treatment period is 12 months and can be renewed if there is no evidence of disease progression	Pirfenidone: The recommended daily oral dose for patients with IPF is 801 mg three times a day with food, for a total of 2403 mg/day. From treatment initiation, the dose should be titrated to the recommended daily dose of 2403 mg per day over a 14-day period as follows: • Days 1 to 7: a dose of 267 mg administered three times a day (801 mg per day) • Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg per day) • Day 15: a dose of 801 mg administered three times a day (2403 mg/day) Initial treatment period is 12 months and can be renewed if there is no evidence of disease progression
Comparator(s)	Best supportive care	
Outcome(s)	Slowed progression of disease as measured by FVC decline over time, resulting in: • Longer survival • Improved quality of life • Avoidance or delay of lung transplants for a small number of individuals.	

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.

9.36. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pirfenidone if it were to be funded in New Zealand for patients with PFILDs for whom nintedanib is not tolerated. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with PFILDs for whom nintedanib is not tolerated
Intervention	Pirfenidone
Comparator(s)	Best supportive care
Outcome(s)	Slowed progression of disease as measured by FVC decline over time, resulting in: • Longer survival • Improved quality of life • Avoidance or delay of lung transplants for a small number of individuals.
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.	