PHARMAC
TE PĀTAKA WHAIORANGA

Pharmacology and Therapeutics
Advisory Committee
Objective advice to Pharmac

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 14 May & 15 May 2026

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1. Present

PTAC members
Rhiannon Braund (Acting Chair)
Brian Anderson
Bruce King
Helen Evans
James Le Fevre
John Mottershead
Liza Lack
Matthew Dawes
Matthew Strother
Robyn Manuel
Stephen Munn

Apologies
Elizabeth Dennett

Observers /Guests
Invited Experts for specific items:
Dr Richard Carroll
Dr Marianne Elston
Dr Tanya McWilliams
Dr Lochie Teague
Dr Julia Philips

2. The role of PTAC, Specialist Advisory Committees and meeting records

2.1. This meeting record of PTAC is published in accordance with the Pharmacology and Therapeutics Advisory Committee (PTAC) Terms of Reference 2021, and Specialist Advisory Committees Terms of Reference 2021.

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

2.3. Conflicts of Interest are described and managed in accordance with sections 6.4 of both the PTAC Terms of Reference and Specialist Advisory Committee Terms of Reference.

2.4. PTAC and Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from Specialist Advisory Committees', including the priority assigned to recommendations, when considering the same evidence. Likewise, Specialist Advisory Committees may, at times, make recommendations that differ from PTAC's, or from other Specialist Advisory Committees', when considering the same evidence.

Pharmac considers the recommendations provided by both PTAC and Specialist Advisory Committees when assessing applications.

3. Record of PTAC meeting held 12 February & 13 February 2026

The Committee acknowledged the draft record of the PTAC meeting held on 12 February & 13 February 2026 was in progress.

4. Action Points

There are no action points.

5. Summary of Recommendations

	Pharmaceutical and Indication	Provisional Recommendation
10.3	Mepolizumab for people with inadequately controlled COPD with an eosinophilic phenotype	Decline
11.3	Osilodrostat for people with endogenous Cushing's syndrome, subject to Special Authority criteria	High priority
12.3	Riociguat for people with CTEPH (Chronic Thromboembolic Pulmonary Hypertension), subject to Special Authority criteria	Low priority
13.4	Duloxetine hydrochloride for various conditions, with no funding restrictions	Cost neutral**
14.3	Anacaulase-bcdb for people with thermal burns (deep partial/ full thickness) for eschar removal, subject to access criteria	High priority
15.3	Risdiplam oral tablet for people Spinal Muscular Atrophy types 1-3, subject to existing Special Authority criteria for the liquid preparation	Cost neutral**
16.3	Durvalumab for people with muscle invasive bladder cancer for neoadjuvant and adjuvant treatment, subject to Special Authority criteria	High priority
17.3	Emicizumab for people with moderate severity Haemophilia A with a clinically severe bleeding phenotype, subject to Special Authority criteria	High priority
18.3	Aflibercept 8mg pre-filled syringe for the treatment of visual impairment caused by subfoveal choroidal neovascularisation secondary to age-related macular degeneration and diabetic macular oedema, subject to Special Authority criteria	Cost neutral**

**Cost Neutral – The Committee has recommended this application be funded if the cost is neutral to the provision of the currently funded medicine(s), including the related health system costs

7. Pharmac Update

7.1. The Committee noted the Pharmac Update and acknowledged the introduction of new Pharmac staff.

7.2. The Committee acknowledged the Invited Experts were invited to attend the meeting for three agenda items. The Committee noted that is an approach to specialist input that has been piloted in Rare Disorders Specialist Advisory Committee meetings to provide sub-speciality input and NZ treatment context. Pharmac is continuing to test this initiative. The Committee noted that Observer – Invited Experts will attend to provide their relevant expertise to support the Committee's considerations. Invited Experts will be given an opportunity to share their insights following the discussion lead presentation and participate in the Committee discussion to answer any questions at the invitation of the Chair. Invited experts will not be present when the Committee votes on a recommendation. Invited Experts complete a confidentiality agreement and a declaration of interest to participate in the meeting. Pharmac staff will consider how this approach could be developed and might support other meeting discussions in the future.

7.3. The Committee noted an update about the organisation reset programme from the Reset Programme Manager and acknowledged that more information can be found on the Pharmac Website.

7.4. The Committee noted that preparations for PTAC recruitment for new members are underway and Pharmac staff will keep the Committee updated on progress.

8. Exceptional Circumstances Framework review update

8.1. The Committee discussed the Exceptional Circumstances Framework following a presentation on the current settings and Pharmac's proposed approach to the review.

8.2. The Committee noted that uncertainty remains around how existing funding pathways interact within the Exceptional Circumstances Framework, particularly in relation to overseas treatment and the interface between the High-Cost Treatment Pool and Named Patient Pharmaceutical Assessment (NPPA).

8.3. The Committee considered that framing exceptionality in clinical rather than patient terms may better reflect the purpose of the framework. Members also observed increasing pressure on the definition of exceptionality, with concern that the use of multiple intersecting factors could broaden eligibility beyond the original intent.

8.4. The Committee also noted variability in evidence expectations, application completeness, and the consistency of information provided, and supported greater pre-assessment by Pharmac to ensure panels can focus on decision-making rather than evidence gathering.

8.5. The Committee discussed ethical and societal considerations, including difficulties in achieving consistency and balancing competing factors.

8.6. The Committee also noted that the naming of the pathway may create unrealistic expectations and that variability in application content may contribute to inconsistent outcomes.

9. Specialist Advisory Committee Record

9.1. November 2025 Immunisation Advisory Committee

9.1.1. PTAC reviewed the records of the Immunisation Advisory Committee meeting held on 6 November 2025.

9.1.2. PTAC noted the records including the Advisory Committee's recommendations

9.2. December 2025 Obesity Treatments Advisory Group

9.2.1. PTAC reviewed the records of the Obesity Treatments Advisory Group meeting held on 11 December 2025.

9.2.2. PTAC noted the records including the recommendations from the Advisory Groups

9.3. December 2025 Interim Medical Devices Advisory Group

9.3.1. PTAC reviewed the records of the Interim Medical Devices Advisory Group meeting held on 10 December 2025.

9.3.2. PTAC noted the records including the Advisory Group's recommendations

10. Mepolizumab (Nucala) for inadequately controlled COPD with an eosinophilic phenotype

Application

10.1. The Committee reviewed a widening of access application for mepolizumab for the treatment of inadequately controlled chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype.

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

Recommendation

10.3. The Committee **recommended** that mepolizumab for inadequately controlled COPD with an eosinophilic phenotype be **declined**.

10.4. When making these recommendations:

10.4.1. The Committee noted a high unmet health need in people with eosinophilic COPD, particularly those with persistent exacerbations despite triple inhaled therapy (LABA/ LAMA/ ICS).

10.4.2. The Committee noted that mepolizumab demonstrated modest reductions in moderate exacerbations, but no consistent or statistically significant benefit in severe exacerbations, hospitalisations (>24 hours), or health-related quality of life (HRQoL).

10.4.3. The Committee considered there was uncertainty in the clinical benefit and considered that alternative therapies may offer greater overall impact.

Discussion

Impact on Māori, Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

10.5. The Committee noted that COPD-related hospitalisation and mortality rates vary substantially by ethnicity in Aotearoa New Zealand.

10.5.1. The Committee noted that Māori experience markedly higher rates of COPD hospitalisation (341.1 per 100,000) and mortality (169 per 100,000) compared with the overall population (128.9 and 77 per 100,000, respectively), with elevated hospitalisation rates also observed among Pacific peoples (Telfar-Barnard, et al. 2024).

10.5.2. The Committee noted that these data indicate significant inequities in COPD outcomes across population groups, with Māori experiencing a disproportionately higher burden of severe disease (Health Quality & Safety Commission Te Tāhū Hauora, COPD prevalence, 2024).

10.5.3. Members noted that Māori/Pacific ethnicity is associated with higher blood eosinophil counts among individuals with COPD (Shantakumar, et al. Resp. Invest. 2021;59(4):487-97).

10.6. The Committee further noted that COPD-related hospitalisation and mortality are strongly associated with socioeconomic deprivation in NZ. The Committee noted that hospitalisation rates increase progressively with higher levels of deprivation, reaching more than five times the rate observed in the least deprived populations (NZDep 9–10 RR ~5.17 vs NZDep 1–2 baseline), and that a similar gradient is observed for mortality, with death rates more than twice as high in the most deprived groups (RR 2.49) (Telfar-Barnard, et al. 2024).

Background

10.7. The Committee noted mepolizumab is currently funded for two indications in NZ, eosinophilic granulomatosis with polyangiitis (EGPA) and severe refractory eosinophilic asthma.

10.7.1. The Committee further noted that mepolizumab is currently under assessment for chronic rhinosinusitis with nasal polyps, and proposals to the widen access for eosinophilic asthma are on the Options for Investment list.

10.8. The Committee noted mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against human interleukin-5 (IL-5).

Health need

10.9. The Committee noted that COPD is a heterogeneous lung condition characterised by persistent, often progressive airflow obstruction due to abnormalities of the airways and/or alveoli, and is typically managed with inhaled therapies, such as long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS).

10.10. The Committee noted that COPD affects a substantial number of people in NZ, with approximately 70,000 individuals currently diagnosed and actively seeking care. The Committee noted that COPD predominantly affects older adults, with the vast majority of cases occurring in people aged 45 years and over, reflecting the progressive and age-related nature of the disease.

10.10.1. The Committee noted that, based on international real-world data (Benson, et al. Int J Chron Obstruct Pulmon Dis. 2019;14:2711-23), approximately 22.3% of people with COPD are receiving triple therapy, that approximately 13.5% of COPD patients continue to experience frequent exacerbations despite triple therapy (≥2 moderate or ≥1 severe in the preceding 12 months), and approximately 6.2% of the total COPD population also have a blood eosinophil count (BEC) of ≥300 cells/μL. The Committee noted this was similar to the supplier estimate that 7.12% of people with COPD would meet the proposed criteria for mepolizumab. The Committee estimated that given that 70,000 individuals in New Zealand have diagnosed COPD, this equates to approximately 4,300 individuals in New Zealand.

10.10.2. The Committee noted that people with severe eosinophilic COPD (eg BEC ≥150 cells/μL and frequent exacerbations despite triple therapy) experience a higher clinical burden than those with non-eosinophilic COPD, including substantially higher rates of moderate and severe exacerbations, increased all-cause mortality, greater primary care utilisation, and higher rates of non-exacerbation-related hospitalisations (Müllerova, et al. Int. J Chron Obstruct Pulmon Dis. 2019;14:741-55).

10.11. The Committee noted that approximately 20–40% of people with COPD have an eosinophilic phenotype (eg eosinophils ≥ 150 cells/μL), which is associated with increased exacerbations (Chen, et al. PLoS One. 2024;19(10):e0302318);(Yun, et al. J Allergy Clin Immunol. 2018;141(6):2037-47), hospital readmissions (Couillard, et al. Chest. 2017;151(2):366-373), reduced quality of life (Benson, et al. Int J Chron Obstruct Pulmon Dis. 2019;14:2711-23) and increased mortality (Müllerová, et al. Int J Chron Obstruct Pulmon Dis. 2019;14:741-55).

10.12. The Committee noted that COPD exacerbations are associated with significant morbidity and mortality, with one-year mortality after a hospitalisation estimated at approximately 20–25% (Hurst et al. Eur J of Int Med. 2020;73:1-6) and five-year mortality exceeding 50% in some cohorts (McGhan, et al. Chest. 2007;132(6):1748-55), and that recurrent exacerbations contribute to disease progression, declining lung function, and reduced quality of life.

10.13. The Committee noted that BEC in COPD demonstrate variability over time, with implications for phenotype classification and treatment selection.

10.13.1. The Committee noted that a review of type 2 biomarkers in COPD (Oishi, et al. J. Clin. Med. 2020;9(8):2670) highlights the heterogeneity of eosinophilic inflammation and limitations of a single timepoint measurement.

10.13.2. The Committee further noted that the following studies assessing the prevalence of elevated blood eosinophils (commonly ≥300 cells/μL) report broadly consistent findings, with approximately 15–25% of patients demonstrating elevated levels across cohort and trial populations.

- Cassanova, et al. Eur. Resp. J. 2017;50(5):1701162
- Watz, et al. Lancet Resp. Med. 2016;4(5):390-98
- Suzuki, et al. AJRCCM. 2016;194(11):1358-65

10.14. The Committee noted that COPD, including eosinophilic COPD, is associated with a substantial impact on health-related quality of life (HRQoL), reflecting the overall burden of disease described in the GOLD 2026 Report (GOLD, 2026).

10.15. The Committee noted that COPD is a leading contributor to disability globally, measured through disability-adjusted life years (DALYs), which capture both premature mortality and

years lived with disability. The Committee further noted that COPD is characterised by persistent symptoms, including breathlessness, cough, and sputum production, which impair daily functioning and often require ongoing symptom management, psychosocial support, and assistance with activities of daily living (Farquar, et al. Chron Respir Dis. 2017;15(1):26-35). The Committee also noted that comorbidities and exacerbation, including those requiring hospitalisation, contribute further to reduced quality of life and increased disease burden. The Committee also noted that COPD impacts family and whānau, impacting mobility and having a psychological impact (Mi, et al. Int J Chron Obstruct Pulmon Dis. 2017;12:2813-21).

10.16. The Committee noted that there remains a high unmet health need for people with eosinophilic COPD in NZ, with evidence of higher rates of hospital admissions and readmissions compared with OECD countries (National health Committee [NHC], 2014), and persistent inequities in disease burden, including higher prevalence, hospitalisation, and mortality rates in priority populations.

Health benefit

10.17. The Committee noted that the current treatment pathway for COPD in NZ follows a stepwise escalation from bronchodilator monotherapy to dual and triple inhaled therapy. The Committee noted that inhaled triple therapy (LAMA, LABA, ICS) is typically used as the final step in the treatment pathway for people with persistent symptoms or recurrent exacerbations.

10.17.1. The Committee noted that the supplier seeks listing of mepolizumab as an add-on maintenance therapy for adults with COPD with an eosinophilic phenotype, defined by a blood eosinophil count great than 300 cells/μL, who have experienced either two exacerbations requiring oral corticosteroids or at least one exacerbation requiring hospitalisation in the previous 12 months.

10.18. The Committee noted the METREX and METREO (Pavord, et al. N Eng J Med. 2017;377:1613-29), two phase 3 trials, multicentre, randomised, double-blind, placebo-controlled, parallel-group trials evaluating subcutaneous mepolizumab as add-on therapy in COPD.

10.18.1. The Committee noted that the trials enrolled adults aged ≥40 years with COPD and a history of frequent exacerbations despite receiving inhaled glucocorticoid-based triple maintenance therapy, including patients with an eosinophilic phenotype defined by BEC thresholds (≥150 cells/mm^3 at screening or ≥300 cells/mm^3 in the prior 12 months).

10.18.2. The Committee noted that the proportion of participants with higher BEC counts (≥300 cells/mm^3 in the previous 12 months) varied across the trial populations, at 9–11% in the overall METREX population, 17–19% in the METREX eosinophilic phenotype subgroup, and 45–48 % in the METREO population, consistent with the differing eligibility criteria applied in each study.

10.18.3. The Committee noted that in METREX, participants were randomised (1:1) to receive mepolizumab 100 mg subcutaneously every four weeks or placebo, while in METREO, participants were randomised (1:1:1) to receive mepolizumab 100 mg, mepolizumab 300 mg or placebo, with treatment administered for 52 weeks in addition to standard of care.

10.18.4. The Committee noted that the primary outcome in both trials was the annualised rate of moderate or severe exacerbations. In METREX, among patients with an eosinophilic phenotype, the rate of moderate or severe exacerbations was lower with mepolizumab compared with placebo (1.40 vs 1.71 events/year; rate ratio 0.82, 95% CI 0.68–0.98; p=0.04), while no

significant difference was observed in the overall population (eosinophilic plus non-eosinophilic population).

10.18.5. The Committee noted that in METREO, reductions in moderate or severe exacerbation rates with mepolizumab were not statistically significant compared with placebo (100 mg: 1.19 vs 1.49 events/year, rate ratio 0.80; 95% CI 0.65–0.98; p=0.07; 300 mg: rate ratio 0.86; 95% CI 0.70–1.05; p=0.14).

10.18.6. The Committee noted that mepolizumab increased time to first moderate or severe exacerbation in METREX among patients with an eosinophilic phenotype (median 192 days vs 141 days; hazard ratio 0.75, 95% CI 0.60–0.94), but no statistically significant improvements were observed in METREO.

10.18.7. The Committee noted that there were no differences between mepolizumab and placebo for exacerbations requiring emergency department visits or hospitalisation, for quality of life measured using the St George's Respiratory Questionnaire (SGRQ), or patient-reported symptoms measures using the COPD Assessment Test (CAT).

10.18.8. The Committee noted that the safety profile of mepolizumab was similar to that of placebo, with comparable rates of adverse events, serious adverse events and mortality across treatment groups.

10.19. The Committee noted the MATINEE trial (Sciurba, et al. N Eng J Med. 2025;392:1710-20), a phase 3, multicentre, randomised (1:1), double-blind, placebo-controlled, parallel-group trial.

10.19.1. The Committee noted that the study enrolled 804 adults aged ≥40 years with COPD receiving inhaled triple therapy, with a BEC of ≥300 cells/μL at screening and a documented historical BEC of ≥150 cells/μL and >=2 moderate exacerbations or >=1 severe exacerbation in the prior 12 months. The population was predominantly male (69%), predominantly Caucasian (84%), with a mean age of 66.2 years, and with 61% aged ≥65 years. The Committee noted key exclusions included asthma and other significant respiratory conditions.

10.19.2. The Committee noted that participants were randomised to receive mepolizumab 100 mg subcutaneously every four weeks plus standard of care (n=403), or placebo plus standard of care (n=401).

10.19.3. The Committee noted that the primary outcome was the annualised rate of moderate or severe exacerbations over 52 to 104 weeks, , which was lower with mepolizumab (0.80 events/year) compared with placebo (1.01 events/year), corresponding to a rate ratio of 0.79 (95% CI 0.66–0.94; p=0.01).

10.19.4. The Committee noted that while mepolizumab reduced the combined rate of moderate or severe exacerbations by approximately 20% compared with placebo, in an exploratory analyses there was nostatistically significant reduction in severe exacerbations alone (0.10 vs 0.15 events/year; RR 0.66, 95% CI 0.43–1.01), although results numerically favoured mepolizumab. The Committee further noted no meaningful difference in lung function (FEV_1).

10.19.5. The Committee noted that mepolizumab increased the time to first moderate or severe exacerbation (median 419 days vs 321 days; hazard ratio 0.77, 95% CI 0.64–0.93; p=0.009). The Committee further noted that exacerbations requiring emergency department (ED) visit or hospitalisation were lower with mepolizumab (0.13 vs 0.20 events/year; RR 0.65, 95% CI 0.43–0.96).

10.19.6. Pertaining to COPD-related quality of life, the Committee noted that there was no statistically significant difference in the COPD assessment test (CAT) response (41% vs 46%; OR 0.81, 95% CI 0.60–1.09). The Committee noted a numerically higher response in St. George's Respiratory Questionnaire (SGRQ) (50% vs 46%; OR 1.17, 95% CI 0.87–1.57).

10.19.7. The Committee noted that the trial was conducted during the COVID-19 pandemic, which may have reduced exacerbation rates and affected treatment effect estimates.

10.20. The Committee noted the COPD-HELP trial (Flynn, et al. NEJM Evid. 2025;4(6):EVIDoa2500012), a phase 2b, single-centre, randomised, double-blind, placebo-controlled trial evaluating mepolizumab initiated following hospitalisation for acute exacerbation of COPD (AECOPD).

10.20.1. The Committee noted that the study enrolled 238 adults aged ≥40 years hospitalised with AECOPD, with evidence of eosinophilic inflammation (≥300 cells/μL in the prior 12 months). The Committee noted the population had severe disease, with a mean age of 69.1 years, high comorbidity burden (median four comorbidities), frequent prior exacerbations, and the majority receiving triple inhaled therapy.

10.20.2. The Committee noted that participants were randomised (1:1) to receive mepolizumab 100 mg subcutaneously every four weeks or placebo for 48 weeks, with treatment initiated at or shortly after hospital discharge.

10.20.3. The Committee noted that the primary outcome was time to hospital readmission or death from any cause, which did not differ between groups (median 25.4 vs 26.1 weeks; hazard ratio 0.96, 95% CI 0.70–1.32; p=0.811).

10.20.4. The Committee noted that hospital readmissions were similar between groups (1.65 vs 1.85 events; rate ratio 0.89, 95% CI 0.64–1.25), with no apparent difference in secondary time-to-event outcomes including respiratory-related readmission or death.

10.20.5. The Committee noted that the rate of severe exacerbations was numerically lower with mepolizumab (2.80 vs 3.45 events; rate ratio 0.81, 95% CI 0.66–1.00), although the upper bound of the confidence interval included no effect.

10.20.6. The Committee noted that there were no meaningful difference in patient-reported outcomes including the SGRQ-C and CAT, physical performance measures, or dyspnoea scores between groups.

10.20.7. The Committee noted that mepolizumab significantly reduced blood eosinophil counts compared with placebo, but this did not translate into improvements in clinical outcomes such as readmission or mortality.

10.21. The Committee noted that mepolizumab may provide modest clinical benefit for people with eosinophilic COPD, including reductions in moderate exacerbations (approximately 20%), associated oral corticosteroid or antibiotic use, and emergency department presentations. However, the Committee considered that there was no improvement in severe exacerbations demonstrated, nor any reduction in longer hospitalisations (>24 hours), health-related quality of life, lung function, or mortality. The Committee further noted that longer-term studies may be required to fully characterise benefits, and that the magnitude of effect appears less than that observed in severe eosinophilic asthma.

10.22. The Committee considered that the available evidence does not support the supplier's economic model assumption that initiating mepolizumab would result in an average gain of [redacted] years of life. The Committee considered that a mortality benefit has not been

demonstrated in the current evidence base and considered there to be insufficient evidence to support the projected survival gain.

10.23. The Committee noted that reduction in COPD-related mortality is an important clinical outcome, particularly given the high mortality risk following hospitalisation for exacerbations. However, the Committee noted that mortality effects are difficult to directly assess in this population and that current clinical trials of mepolizumab are of insufficient duration, with no evidence currently demonstrating a treatment effect on mortality.

10.24. The Committee noted that the overall quality of the evidence is moderate, supported by large randomised, placebo-controlled and blinded studies, with some supporting real-world data, but with limitations including potential risk of bias due to industry sponsorship and uncertainty regarding longer-term outcomes.

Suitability

10.25. The Committee noted mepolizumab is given as a subcutaneous injection, 100 mg every four weeks, and that administration may be undertaken by patients themselves or with assistance from whānau or carers. The Committee noted that appropriate education and training would be required to ensure correct storage and administration technique, including instruction on injection sites and rotation of sites to minimise local reactions.

Cost and savings

10.26. The Committee was made aware of a cost-effectiveness analysis (Buendía, et al. BMC Pulm. Med. 2026;26:101), which used a Markov model simulating a COPD cohort aged ≥40 years over a lifetime horizon, with clinical inputs derived from pooled randomised trial data. The Committee considered the model to present a plausible model of the disease.

10.26.1. The Committee noted that mepolizumab was associated with an approximately 14% relative reduction in exacerbation risk; however, the incremental cost-effectiveness ratio was estimated at $45,192 USD per QALY gained, substantially exceeding the Colombian willingness-to-pay threshold, with a 0% probability of meeting that threshold and being considered cost-effective.

Funding criteria

10.27. The Committee noted that BEC in COPD demonstrate variability over time. In considering eligibility criteria, the Committee noted that the MATINEE trial required BEC ≥300 cells/µL at screening and ≥150 cells/µL at an earlier timepoint (eg within the previous year, or at baseline). However, Members considered that an alternative approach may be more appropriate, with BEC ≥150 cells/µL at the time of assessment and documentation of BEC ≥300 cells/µL at any point within the previous 12 months.

10.28. The Committee was made aware of the BOREAS study (Bhatt, et al. New Eng J Med. 2023;389:205-14) and NOTUS study (Bhatt, et al. New Eng J Med. 2024;390:2274-83), two trials which evaluated dupilumab, a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation.

10.28.1. The Committee noted that dupilumab demonstrated reductions in exacerbation rates in patients with COPD and an eosinophilic phenotype (approximately 30–34%), with modest improvement in lung function (FEV_1) (Donohue. COPD. 2005;2:111-24), and inconsistent or non-significant improvements in HRQoL (Jones, et al. Chronic Obstr Pulm Dis. 2017;4(2):124-131).

10.29. The Committee noted an indirect treatment comparison (Bhatt, et al. Pulm Ther. 2025;12(1):201-17) evaluating the relative efficacy of dupilumab versus mepolizumab in people with COPD and a type 2 inflammatory (eosinophilic) phenotype, which suggested

numerically greater reductions in exacerbations and improvements in lung function and symptoms with dupilumab compared with mepolizumab, although differences were not consistently statistically significant and findings were subject to uncertainty due to the indirect study design.

10.30. The Committee expressed interest in reviewing dupilumab for the treatment of COPD with an eosinophilic phenotype, should a supplier be willing to enter the NZ market and pursue a funding application.

11. Osilodrostat for endogenous Cushing's syndrome

Application

11.1. The Committee reviewed the supplier application from Recordati Rare Diseases Australia Pty for osilodrostat in the treatment of endogenous Cushing's syndrome in adult patients.

11.1.1. The Committee noted that the funding application for osilodrostat has been accepted under Pharmac's policy principles for Rare Disorders, and that Pharmac defines rare disorders as conditions affecting fewer than 1 in 2,000 people.

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

Recommendation

11.3. The Committee **recommended** that osilodrostat be listed for the treatment of endogenous Cushing's syndrome in adult patients with a **high priority**, subject to the following Special Authority criteria:

> Initial Application (endogenous Cushing's syndrome) – from an Endocrinologist or any relevant practitioner on the recommendation of an Endocrinologist. Approval valid for 6 months.
> All of the following:
> 1. Patient has active endogenous Cushing's syndrome; and
> 2. Either:
> 1. Patient has persistent or recurrent hypercortisolism after surgery; or
> 2. Patient is not a candidate for surgery; and
> 2. Either:
> 2.1. Patient has received insufficient benefit from metyrapone, whether due to lack of efficacy or tolerability; or
> 2.2. Metyrapone is contraindicated for this patient.
>
> Renewal (endogenous Cushing's syndrome) – from an Endocrinologist or any relevant practitioner on the recommendation of an Endocrinologist. Approval valid for 12 months.
> 1. Patient has received a complete or partial response after at least 6 months of treatment.
>
> Note: A complete response is defined as a mean urinary free cortisol (UFC) level of less than or equal to the upper limit of normal (ULN). A partial response is defined as mean UFC level of greater than ULN but with at least 50% reduction from the baseline value. The mean UFC should be the average of at least two urine samples.

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

11.4.1. Cushing's syndrome is a severe condition with significant morbidity, mortality risk, and reduced quality of life, particularly in acutely unwell patients.

11.4.2. Existing therapies may be poorly tolerated, less effective, or unsuitable for a subset of patients, leaving a clear clinical and health need gap.

11.4.3. Osilodrostat has a demonstrated ability to control cortisol levels, with a reasonable expectation this translates to improved clinical outcomes.

11.4.4. Osilodrostat may support Cushing's syndrome management in key settings (e.g. post-surgical failure), where timely and effective treatment is essential.

Discussion

Patient lived experience

11.5. The Committee noted and acknowledged a patient submission highlighting diagnostic delays of several years, with a range of health issues later attributed to Cushing's disease. The submission emphasised the physical and psychological impact of Cushing's disease on the individual, their family and friends; the significant and lasting impact on the individual from the effects of treatment; and the implications for the individual's ability to work and plan their future.

11.6. The submission reflected the severe and debilitating symptoms and multi-system comorbidities due to prolonged cortisol excess in Cushing's disease, and its significant impact on quality of life. The Committee considered that while access to specialist care is limited across New Zealand, accurate diagnosis of Cushing's syndrome is complex and that that existing therapies for Cushing's syndrome in New Zealand may be poorly tolerated, less effective, or unsuitable for a subset of patients, leaving a clear patient health need.

11.7. The Committee expressed sincere appreciation to the individual for their submission describing their experience with the impacts of Cushing's disease and its treatment. The Committee acknowledged the courage required to share their personal story.

Māori impact

11.8. The Committee discussed the impact of osilodrostat for the treatment of Cushing's syndrome on Māori health areas of focus and Māori health outcomes.

11.9. The Committee noted the New Zealand-based study by Bolland et al. Clin Endocrinol (Oxf). 2011;75:436-42) which includes ethnic distributions reflective of the local population, particularly with respect to Māori and Pacific peoples.

11.9.1. The Committee did not consider Cushing's syndrome to disproportionately affect Māori, however, considered that access to specialist endocrinology services and tertiary care may contribute to inequities in management and outcomes. The Committee noted that there are no data to suggest a specific impact on Māori health outcomes.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

11.10. The Committee discussed the impact of Cushing's syndrome on Māori, Pacific peoples, disabled people, and other people who have been underserved by the health system.

11.10.1. The Committee considered that patients in rural settings and Pacific peoples may experience barriers to accessing specialist care, which could impact diagnosis and treatment. The Committee noted that there is no data to indicate a specific impact from Cushing's syndrome for other groups experiencing health inequities.

Health need

11.11. The Committee noted that Cushing's syndrome describes a collection of signs and symptoms arising from prolonged exposure to excess cortisol, a steroid hormone normally produced by the adrenal glands, and that endogenous Cushing's syndrome comprises a heterogeneous group of rare diseases resulting from the body's overproduction of cortisol (Nieman et al. J Clin Endocrinol Metab. 2015;100:2807–31).

11.12. The Committee noted that the majority of patients with endogenous Cushing's syndrome have a pituitary source of adrenocorticotropic hormone (ACTH) leading to excess cortisol production (ie Cushing's disease), while other causes include ectopic ACTH secretion or ACTH-independent cortisol production from an adrenal source (Nieman et al. 2015).

11.13. The Committee noted that Cushing's syndrome can cause severe and debilitating symptoms and multi-system comorbidities due to prolonged cortisol excess, and that untreated disease is associated with increased morbidity and mortality (Nieman et al. 2015; Nieman et al. J Clin Endocrinol Metab. 2008;93:1526–40). The Committee considered that there is a consequential reduced quality of life in Cushing's syndrome that is particularly impactful in acutely unwell patients.

11.14. The Committee considered that patients with ectopic Cushing's syndrome are typically extremely unwell, with high mortality driven by complications such as opportunistic infections (eg pneumocystis infection) and vascular disease.

11.15. The Committee noted the risk of complications of Cushing's syndrome such as myopathy (for which there are no funded treatments), neuropsychiatric effects, and thrombotic events (which may be managed with anticoagulation) (Nieman et al. 2015). The Committee noted that neuropsychiatric effects can have a significant impact on quality of life (Nieman et al. 2015).

11.16. The Committee considered that the prevalence of Cushing's syndrome is increasing, and estimated an incidence of approximately 5 to 10 new cases per million per year. The Committee considered that a multidisciplinary service covering approximately one million people sees around 10 to 15 new cases each year. The Committee considered that approximately 50 new cases, with a possible range of 25 to 75, may occur annually in New Zealand. The Committee considered that the presentation of Cushing's syndrome is evolving and that this also has an influence on the increasing prevalence:

11.16.1. The Committee considered that there is an increasing recognition of adrenal Cushing's syndrome, with adrenal nodules being detected more frequently and considered this is often associated with milder forms of hypercortisolism.

11.16.2. The Committee considered there is a broader trend in endocrinology where classical descriptions of endocrine disorders were largely based on overt disease and clear biochemical abnormalities, but over time, it has become evident that the phenotype is more variable. The Committee considered that for Cushing's syndrome, some individuals present with classical and overt hypercortisolaemia but exhibit relatively mild symptoms compared with the traditional clinical picture.

11.16.3. The Committee considered that these factors are likely to change how Cushing's syndrome is characterised, contributing to an apparent increase in prevalence and influencing long-term outcomes due to the inclusion of more diverse patient cohorts.

11.17. The Committee noted that delays in diagnosis are common, with some patients experiencing symptoms for several years prior to diagnosis (Valassi et al. Endocr Connect. 2022;11:e220027). The Committee considered that delays in treatment are

also common and may relate to the time required to complete comprehensive diagnostic work-up, including imaging and exclusion of ectopic disease, as well as access to specialist surgical services.

11.18. The Committee considered that treatment of Cushing's syndrome in New Zealand predominantly involves surgery (undertaken in tertiary centres with relevant expertise) to remove the pituitary tumour where this is driving cortisol overproduction, with subsequent options including medical therapy, repeat surgery, radiation therapy or adrenal resection where remission is not achieved.

11.18.1. The Committee noted that pituitary surgery is the preferred initial treatment for patients with a pituitary source of ACTH-dependent Cushing's syndrome, with remission evaluated by cortisol levels (Fleseriu et al. Lancet Diabetes Endocrinol. 2021;9:847–75).

11.18.2. The Committee considered that waiting times for pituitary surgery can be prolonged (often six to nine months) and that outcomes are generally better when surgery is performed by experienced pituitary surgeons, of whom there are relatively few in New Zealand.

11.19. The Committee considered that some patients may prefer oral medical therapy instead of surgery, including individuals concerned about the potential effects of pituitary surgery on fertility or those who wish to avoid major surgery.

11.20. The Committee noted that the 2021 International Pituitary Society guidelines recommend bilateral adrenal resection often as a last-resort treatment option, due to its significant lifelong implications including the requirement for ongoing glucocorticoid and mineralocorticoid replacement therapy.

11.21. The Committee noted that the limited oral treatments available for long-term management of Cushing's syndrome in New Zealand include metyrapone and ketoconazole, with ketoconazole being used outside its Medsafe-approved indications. The Committee noted that these agents exert their effects at the adrenal level and as this is an endocrine pathway, inhibition at some steps can lead to accumulation of upstream intermediates, which is relevant to the potential side effects associated with blockade therapy (Fleseriu et al. 2021).

11.22. The Committee considered that medical therapy plays an important role in achieving preoperative biochemical control, improving symptoms, and optimising patients for surgery.

11.22.1. Rapid medical blockade of cortisol is critical while the source of ACTH production is being identified in some patients with ectopic Cushing's syndrome (Nieman et al. 2015).

11.22.2. Some patients require pre-operative medical therapy, while others may proceed directly to definitive treatment or present with relatively mild disease (Fleseriu et al. 2021).

11.22.3. Evolving treatment approaches including increased use of medical therapies may reduce the need for bilateral adrenalectomy.

11.22.4. A small proportion of patients require long-term medical management, based on clinical experience (eg patients who have not undergone surgery or who are not suitable candidates for surgery). The Committee acknowledged the small size of this cohort and the limited evidence of long-term outcomes with medical therapy alone.

11.22.5. The Committee noted that the use of metyrapone may result in clinically significant adverse effects including hypertension, hypokalaemia and hirsutism (Nieman et al. 2015), and considered that these effects might make it less favourable, particularly in the context of ectopic Cushing's syndrome.

11.22.6. The Committee noted the numerous drug interactions with ketoconazole and considered this may limit its use to predominantly short-term use for severe Cushing's syndrome. The Committee noted that ketoconazole may also be associated with adverse endocrine effects, including altered androgen activity and hypogonadism in men, as well as variable absorption due to dependence on gastric acidity (Fleseriu et al. 2021).

11.22.7. The Committee acknowledged that while metyrapone may achieve biochemical control in approximately 70% of patients (Fleseriu et al. 2021), this effect can diminish over time in clinical practice, potentially necessitating dose escalation and increasing the risk of adverse effects.

11.22.8. The Committee acknowledged that tolerability depends on an individual's adverse effect profile and that metyrapone may remain an appropriate option for some patients within the population under discussion.

11.23. The Committee noted that radiotherapy can result in hypopituitarism (Fleseriu et al. 2021), and considered that this may have a significant impact on quality of life and contribute to increased mortality risk. The Committee also considered the potential associated cost to the healthcare system, particularly in cases where patients require long-term hormone replacement such as daily growth hormone therapy. The Committee further considered that radiation therapy may damage the optic chiasm, including causing vision loss where tumours are located nearby. The Committee also noted risks of secondary malignancy and stroke (Fleseriu et al. 2021), considered that these risks may be greater with older radiotherapy techniques, and noted that patients may already have an elevated baseline risk of cerebrovascular events (Fleseriu et al. 2021).

11.24. The Committee noted that therapies targeting pituitary ACTH production are either in development, not yet widely applicable in clinical practice, or have only partial efficacy, such as pasireotide. The Committee also noted that cabergoline has limited efficacy in this setting (Fleseriu et al. 2021).

11.25. The Committee considered that patients who require ongoing therapy typically undergo extensive long-term follow-up. The Committee noted that ongoing management includes monitoring and optimisation of risk factors such as potassium levels, bone health, and cardiovascular risk, as well as consideration of further surgical intervention (Nieman et al. 2015).

11.25.1. The Committee noted that patients often require continued follow-up even after apparent cure, as recovery following control of hypercortisolism may be prolonged and some symptoms and health effects may persist for months or years (Nieman et al. 2015).

11.25.2. The Committee noted the importance of monitoring for longer-term complications, including dysglycaemia, cardiovascular disease, bone health, and potential future endocrine dysfunction related to prior treatments (Nieman et al. 2015).

11.26. Overall, the Committee considered that existing therapies for Cushing's syndrome in New Zealand may be poorly tolerated, less effective, or unsuitable for a subset of patients, leaving a clear clinical gap and patient health need.

11.27. The Committee considered that concomitant conditions such as hypertension and diabetes in people with Cushing's syndrome are usually managed through standard of care via established health system care pathways.

Health benefit

11.28. The Committee noted that osilodrostat inhibits enzymes involved in adrenal cortisol synthesis and also partially inhibit pathways involved in aldosterone and androgen production. The Committee noted that osilodrostat is proposed to be used as a long-term medical therapy for Cushing's syndrome and is expected to be effective across this heterogeneous group irrespective of the underlying disease aetiology (ie pituitary, ectopic or adrenal), although the clinical trial evidence for osilodrostat is primarily in Cushing's disease.

11.29. The Committee noted the key evidence for osilodrostat from LINC-4: a phase 3, randomised (2:1), double-blind study and open-label period including 73 adults with Cushing's disease requiring medical therapy, and its longer-term extension (Gadelha et al. J Clin Endocrinol Metab. 2022;107:e2882-95; Gadelha et al. Front Endocrinol (Lausanne). 2023:14:1236465).

11.29.1. The Committee noted that LINC-4 participants received osilodrostat 2 mg BD (titrated) or placebo during the 12-week double-blind study period followed by a 36-week open-label period. The Committee noted that LINC-4 was industry-sponsored and considered the trial was of good quality with appropriate endpoints.

11.30. The Committee noted that at week 12 the primary endpoint of the proportion of participants with mean urinary free cortisol (mUFC) at or below the upper limit of normal (ULN) was 77% with osilodrostat compared to 8% with placebo (odds ratio: 43; $p<0.0001$). The Committee noted that the median time to control was about 35 days; that at week 36, 80.8% were controlled; and at week 48, 68.5% were complete responders and 11% partial responders (Gadelha et al. 2022).

11.31. The Committee also noted evidence from LINC-3, a phase 3 open label study with a randomised withdrawal period involving 137 adults with Cushing's disease who received osilodrostat initiated at 2 mg BD (and titrated to a maximum dose of 30 mg BD) for 48 weeks (Pivonello. et al. J Endocrinol Invest. 2024;47:2437-48; Pivonello et al. Lancet Diabetes Endocrinol. 2020;8:748–61) and subsequent analyses of LINC-3 and pooled data from 210 participants from LINC-3/4 who received a median osilodrostat dose of 6.8 mg/day for up to 72 weeks (Fleseriu.et al. Pituitary. 2025;28:22).

11.32. The Committee noted that the LINC trials reported a durable effect of osilodrostat on cortisol levels over a 108-week period, with normal or near normal cortisol achieved across all baseline mUFC levels and no evidence of waning efficacy over the observed period (Fleseriu et al. Eur J Endocrinol. 2022;187:531-41; Gadelha et al. 2023). However, the Committee acknowledged that longer-term evidence remained limited.

11.33. The Committee considered that osilodrostat could be continued where it is tolerated and produced a clinically meaningful reduction in cortisol, even if full normalisation was not achieved.

11.34. The Committee noted that the adverse effects of osilodrostat were generally consistent with its mechanism of action, although acknowledged that adrenal insufficiency or hypocortisolism may occur and require careful dose titration and monitoring. The Committee considered that adverse effects associated with steroid-precursor accumulation, including hypertension, hypokalaemia, hirsutism and acne, may occur less frequently with osilodrostat than with metyrapone.

11.35. The Committee considered that the available health-related quality of life (HRQoL) data with osilodrostat were limited and that improvements during the trial follow-up periods were modest. The Committee considered that, given recovery after biochemical control may take months or years, meaningful improvements in quality of life may therefore not be captured during relatively short clinical trial follow-up.

11.36. The Committee noted that no published prospective head-to-head trial comparing osilodrostat with an active comparator was available at the time of its consideration.

11.37. The Committee noted that there was no direct evidence from high-quality studies that treatment with osilodrostat improved survival. The Committee noted that descriptive registry studies suggested lower standardised mortality ratios (SMRs) among people who achieved biochemical remission, predominantly following surgical treatment, compared with those with persistent disease.

11.37.1. The Committee noted that published SMRs varied across studies and according to remission status and the populations included. The Committee questioned whether the SMR of 6.9 for those not in remission (Ragnarsson et al. J Clin Endocrinol Metab. 2019;104:2375-2384) was the most appropriate estimate for economic assessment and considered that older New Zealand data reporting an overall SMR of 4.1 may provide a relevant alternative source (Bolland et al. Clin Endocrinol (Oxf). 2011;75:436-42).

11.38. The Committee considered it reasonable to assume, over the timeframes considered in the economic assessment, that normalisation of cortisol with osilodrostat may be associated with survival outcomes similar to those following biochemical remission. However, the Committee acknowledged that this was inferred from descriptive evidence predominantly relating to surgically achieved remission and remained uncertain.

11.39. The Committee noted emerging evidence suggesting that osilodrostat may have a more rapid onset of action compared with metyrapone (Detomas et al. Front Endocrinol (Lausanne). 2022:13:903545; Hickey et al. Adv Ther. 2025;42:3472-85). The Committee considered that osilodrostat may support Cushing's syndrome management in key settings (e.g., post-surgical failure) where timely and effective treatment is essential; that it may reduce reliance on adrenal resection; and that it may have a meaningful role in pre-operative stabilisation.

11.40. The Committee acknowledged that the submission proposed additional benefits from osilodrostat including reductions in cardiovascular risk and associated events, as well as other complications. The Committee noted that given the availability of alternative funded interventional strategies for concomitant conditions, it is difficult to quantify any incremental benefit and considered that the evidence supporting improvements in lipid control, blood pressure, and diabetes outcomes was limited. The Committee considered that any advantage may be limited to a marginal reduction in overall treatment burden through improved cortisol control.

11.41. Overall, the Committee considered that osilodrostat has a demonstrated ability to control cortisol levels, and that it is reasonable to assume that normalisation of cortisol levels would be associated with improved clinical outcomes over the observed timeframes, analogous to remission. However, the Committee noted that this relationship is inferred and cannot be established with certainty.

Suitability

11.42. The Committee considered osilodrostat to be a suitable oral tablet requiring individual dose titration. The Committee noted that osilodrostat is administered twice daily compared with metyrapone which may require dosing up to four times daily, and considered that the less frequent dosing may be advantageous for long-term treatment.

11.43. The Committee considered that monitoring requirements for patients receiving osilodrostat are not substantially different from current practice. The Committee noted that efficacy can be assessed using urinary free cortisol, with additional monitoring of morning serum cortisol to minimise the risk of overtreatment (Fleseriu et al. 2021).

Cost and savings

11.44. The Committee considered that, among people diagnosed and treated for Cushing's syndrome, the number of people requiring long-term medical therapy would be very small. The Committee considered that uptake would likely be higher among incident cases, particularly in patients with more severe or inadequately controlled disease.

11.45. The Committee considered that the health resource use assumptions presented by Pharmac staff appeared reasonable. The Committee noted that successful treatment with osilodrostat would not remove the need for long-term follow-up and management of residual or longer-term health effects (Nieman et al. 2015).

Funding criteria

11.46. The Committee considered that Special Authority applications (both initial and renewal) for osilodrostat should be made by an Endocrinologist or by any other relevant practitioner on the recommendation of an Endocrinologist, reflecting the specialist expertise required to diagnose and treat the condition.

11.47. The Committee considered that the duration of the initial and renewal approvals for osilodrostat should be six and 12 months, respectively, with renewal based on an assessment of benefit occurring after at least six months of treatment with osilodrostat.

11.48. The Committee considered it reasonable to target those who are not candidates for surgery. The Committee further considered that a patient who had declined surgery following specialist assessment should not necessarily be excluded from accessing osilodrostat solely on that basis. The Committee noted that surgery would remain the recommended first-line treatment for pituitary-dependent Cushing's syndrome where clinically appropriate (Fleseriu et al. 2021).

11.49. The Committee noted that the application positioned osilodrostat after inadequate benefit from, intolerance to, or contraindication to, metyrapone. The Committee considered that osilodrostat may be preferred to metyrapone because of its tolerability, less frequent dosing and apparent durability of response, and that it may have an important role in preoperative biochemical control. The Committee considered that there was clinical interest in earlier use of osilodrostat. However, the Committee's recommendation related to the population and place in therapy as proposed in the application and described in the funding criteria.

Summary for assessment

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

Population	People with endogenous Cushing's syndrome (CS), who: - Are not candidates for surgery or for whom surgery was not curative; and - Have experienced insufficient benefit from, are unable to tolerate, or have a contraindication to, metyrapone.
Intervention	Osilodrostat. Starting dose of 1-2 mg twice daily. Dose titration (using a 2-5-10-20-30 mg twice daily dose-escalation sequence) not more frequently than once every 1 -2 weeks (trial titration approximately every 3 weeks) until response to treatment, up to a maximum of 30 mg twice daily. Median key trial dose of approximately 7mg per day in key trials.
Comparator(s)	Continued treatment with metyrapone or ketoconazole (where tolerated and clinically appropriate); otherwise further medical or interventional management according to the patient's treatment pathway.
Outcome(s)	**Response to treatment – normalising mean urinary free cortisol (mUFC)** Defined as having a mUFC excretion ≤ the upper limit of normal (ULN) LINC-4 trial: Week 12 primary endpoint: mUFC ≤ ULN in 77% osilodrostat vs 8% placebo (OR≈43; p<0.0001). Median time to control: ~35 days; improvements evident ~Week 5. Week 36: 80.8% controlled. Week 48: 68.5% complete responders + 11% partial responders. **Potentially improved mortality rate - associated with sustained biochemical control (inferred and uncertain)** No direct evidence was available that osilodrostat improves survival. In observational studies, standardised mortality ratio (SMR) for people with Cushing's disease was 1.9 (95% CI, 1.5 to 2.3) for people in remission compared to 6.9 (95% CI, 4.3 to 10.4) for those not in remission (Ragnarsson et al. J Clin Endocrinol Metab. 2019;104:2375-2384). Older New Zealand data reporting an overall SMR of 4.1 may provide a relevant alternative source (Bolland et al. Clin Endocrinol (Oxf). 2011;75:436-42). The extent to which these estimates could be applied to biochemical response achieved with osilodrostat was highly uncertain.
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.	

12. Riociguat for CTEPH (Chronic Thromboembolic Pulmonary Hypertension)

Application

12.1. The Committee reviewed the application for riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH).

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

Recommendation

12.3. The Committee **recommended** that riociguat for the treatment of chronic thromboembolic pulmonary hypertension be funded with a **low priority** subject to the following Special Authority criteria:

> **Riociguat**
> **Initial application - Chronic thromboembolic pulmonary hypertension (CTEPH)**
> Applications only from a physician specialising in the treatment of pulmonary hypertension or any relevant practitioner on the recommendation of a physician specialising in the treatment of pulmonary hypertension.
> Either
> 1. Individual has inoperable CTEPH or
> 2. Individual has persistent or recurrent CTEPH after balloon pulmonary angioplasty treatment or pulmonary endarterectomy

12.4. In making this recommendation the Committee considered:

- The high unmet heath need of individuals with CTEPH
- The currently available treatments are used off label and not specific for treating CTEPH
- There is evidence of health benefit from riociguat treatment, however the size of treatment effect is uncertain considering the currently available data
- Riociguat treatment is well tolerated

Discussion

Patient lived experience

12.5. The Committee noted it had received submissions from one patient living with CTEPH. The submission described the individual's personal journey of being diagnosed with CTEPH, their experience of living with the condition and its effects on both themselves and their whānau and friends. It further provided their experience of interacting with the New Zealand healthcare system, and their hopes of the benefits riociguat treatment could provide if funded.

12.6. The Committee wished to express their sincere gratitude to the individual for their submission and recognised the courage of sharing their personal story and experience.

Māori impact

12.7. The Committee discussed the impact of funding treatment of CTEPH on Māori health areas of focus and Māori health outcomes. The Committee noted:

12.7.1. The treatment of respiratory health (romaha ora) is a Hauora Arotahi (Pharmac Māori Health Areas of Focus).

12.7.2. The Committee considered there was a lack of accurate data on the prevalence of pulmonary arterial hypertension (PAH) in New Zealand. The Committee noted that New Zealand patients are due to be included in the New Zealand and Australian registry. The Committee were made aware that analysis of this data would be available in the future, including patient demographics and outcomes.

Populations with high health needs.

12.8. The Committee discussed the health needs of CTEPH among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding riociguat and considered:

12.8.1. The Committee considered there was a lack of data on ethnic disparities for CTEPH.

12.8.2. There was inequity in access to treatment, with one centralised Auckland clinic that specialises in treating CTEPH. The Committee considered many individuals could not easily access the National CTEPH clinic based in Auckland, or balloon pulmonary angioplasty (BPA) surgery that is currently only performed in Melbourne.

12.8.3. The Committee considered access to specialised clinics was particularly hard for those in rural areas, that were frequently managed through telehealth.

Background

12.9. The Committee noted riociguat, and treatments for CTEPH have not previously been considered.

12.9.1. The Committee noted the application was accepted under Pharmac's policy principles for Rare Disorders, and that Pharmac defines rare disorders as conditions affecting fewer than 1 in 2,000 people.

Health need

12.10. The Committee noted that CTEPH is considered as group IV form of pulmonary hypertension, which is defined as being due to chronic thrombotic and/ or embolic disease (Humbert et al. Eur Heart J. 2023;44:1312).

12.11. The Committee noted CTEPH described individuals who are symptomatic with mismatched perfusion defects on ventilation-perfusion (V/Q) scan and with signs of chronic, organised, fibrotic clots and chronic total occlusions (pouch lesions or tapered lesions), after at least three months of therapeutic anticoagulation.

12.12. The Committee considered the applicant noted a subgroup of individuals will have chronic clots but no pulmonary hypertension, and this group would not require treatment with riociguat.

12.13. The Committee noted individuals with CTEPH present at variable ages, however the disease is present equally in both genders at advanced age. The Committee noted individuals may have a history of venous thromboembolism at diagnosis however often present with normal or mildly impaired pulmonary function tests (Humbert et al. 2023).

12.14. The Committee noted the clinician applicant who reported patients often present with unexplained breathlessness post pulmonary embolism whilst some individuals are diagnosed on radiology after presenting with pulmonary hypertension.

12.15. The Committee noted the incidence and prevalence of CTEPH is estimated to be 2–6 and 26–38 cases/million adults, respectively, with the number increasing due to further education and diagnosis of the condition (Humbert et al. 2023).

12.16. The Committee noted a systematic review and meta-analysis reported the incidence of CTEPH is 0.6% in all patients with acute pulmonary embolism (PE), 3.2% in survivors, and 2.8% in survivors without major comorbidities (Ende-Verhaar et al. Eur Respir J. 2017;49:1601792). The Committee considered CTEPH is reported to occur as a sequelae of ~ 2-4% of acute pulmonary embolus usually in the first 2 years although ~ 25% of patients diagnosed with CTEPH will not have a history of vascular thromboembolic disease (Ende-Verhaar et al. Eur Respir J. 2017;49:1601792).

12.17. The Committee considered there were several risk factors associated with development of CTEPH, including: permanent intravascular devices, inflammatory bowel disease,

essential thrombocythemia, polycythaemia, splenectomy, anti-phospholipid syndrome, high dose thyroid replacement and malignancy (Humbert et al. 2023).

12.18. The Committee noted Guillevin et al. Eur Respir Rev. 2013;22:535–42 that performed a large-scale international survey to understand the impact of PAH on patients' and carers' lives. Both the patients and the carers noted that PAH had an effect on employment, inability to work and reduction in household income. The Committee noted the study reported living with PAH affected key areas of life including physical activity, travel and social opportunities, domestic chores and relationship issues. This was reflected in 57% of carers reporting PAH had a profound effect on day to day living, often resulting in feeling exhaustion.

12.19. The diagnosis of pulmonary hypertension is complex, and the average time from symptom onset to diagnosis is >2 years, with many presenting with advanced disease.

12.20. The Committee noted that initial treatment is three months of treatment with a vitamin K antagonist, before progressing to either sildenafil and/ or bosentan treatment, or surgery.

12.21. The Committee considered that most individuals are referred by tertiary pulmonary clinics to the national specialist clinic in Auckland.

12.22. The Committee noted the 2022 European Society of Cardiology (ESC) and the European Respiratory Society guidelines for the treatment of CTEPH.

12.23. The Committee considered all individuals with a CTEPH diagnosis are discussed at a multidisciplinary meeting in Auckland, as well as with clinicians in Melbourne, to consider the most appropriate treatment, including surgery, which consists of either pulmonary endarterectomy (PEA) and / or balloon pulmonary angioplasty (BPA) as well as medical therapy.

12.24. The Committee considered BPA was usually utilised in individuals with more distal disease, which can be up to 3-4 treatments a year often over two years and limited by radiation exposure.

12.25. The Committee considered that while PEA surgery is performed in Auckland, BPA is currently only available in Melbourne; however, this is currently being established in Auckland. The Committee considered that PEA surgery is associated with an extended intensive care unit recovery time.

12.26. The Committee considered individuals may require both PEA and BPA surgery to treat the disease proximally or distally.

12.27. The Committee considered individuals may require a lung transplant if their condition deteriorates.

12.28. The Committee considered individuals would receive medical therapy where they have a pre-operative high pulmonary vascular resistance (>15 woods units/ 1200 dynes), post PEA surgery mean pulmonary artery pressure>35, or those whose disease is not suitable for surgery or are not clinically fit enough to receive surgery.

12.29. The Committee noted that currently funded medical therapies are limited to sildenafil and bosentan however these are used off label, with combination therapy commonly used. The Committee considered that bosentan treatment was associated with a risk of liver toxicity.

12.30. The Committee considered outcomes from surgery were superior to medical therapies and medical therapy was considered the last resort for treatment.

Health benefit

12.31. The Committee noted Ghofrani et al. N Engl J Med. 2013;369:319-29 that reported results from the CHEST trial, a phase 3 multicentre randomised double-blind placebo controlled trial. The Committee noted the following results:

12.31.1. At 16 weeks, individuals treated with riociguat had a mean increase of 39 m in the six-minute walk test compared to a mean decrease of 6 m in the placebo group (least-squares mean difference (LSMD), 46 m; 95% confidence interval [CI], 25 to 67; P<0.001).

12.31.2. Pulmonary vascular resistance decreased by 226 dyn·sec·cm^{-5} in those treated with riociguat, vs increase of 23 dyn·sec·cm^{-5} in the placebo group (LSMD, –246 dyn·sec·cm–5; 95% CI, –303 to –190; P<0.001)

12.31.3. The Committee considered the riociguat was reasonably well tolerated, with headache, dizziness and dyspepsia as the most common side effects.

12.31.4. The Committee considered the majority of trial participants are European, with the majority of the other participants of Asian descent. The Committee considered it reasonable to assume similar health benefit across ethnicities.

12.31.5. The Committee considered the baseline characteristics were well balanced.

12.31.6. The Committee considered the six-minute walk test is useful to compare to determine improvement for the individual after treatment, however there was a large variability in the baseline six-minute walk test across people with CTEPH that is affected by characteristics other than their disease including age, and general fitness.

12.32. The Committee noted Ghofrani et al. Respir Med. 2021:178:106220 that reported results from a study of the safety data in the EXPERT registry.

12.32.1. The Committee considered the trial was powered to evaluate the long-term safety of riociguat, and not efficacy.

12.32.2. The Committee noted the registry was ongoing.

12.32.3. The Committee noted at the time, no single adverse event was observed in more than 12% of participants.

12.33. The Committee noted Held et al. ERJ Open Res. 2025;11:00230 that provided analysis of the COMPERA registry.

12.33.1. The Committee noted this was an ongoing European observational registry that was established in 2007.

12.33.2. The Committee considered the registry included data from approximately 13,000 individuals of which 1451 had CTEPH.

12.33.3. The Committee noted that the study reported an improvement in three- and five-year Kaplan Meier survival estimates. The Committee noted that the authors commented that there was an absence of prospective head-to-head studies and acknowledged that registry data do not hold to the same scientific rigor as randomised clinical trials.

12.34. The Committee considered individuals included in trials were the prevalent population and may be clinically fitter than the New Zealand population. The Committee considered

registry data also includes the incident and prevalent populations and would be more representative of the real-world data.

12.35. The Committee considered overall any improvement in function can be beneficial for individuals with a respiratory disease which has a significant effect on daily life. The Committee considered it was difficult to be confident about the size of treatment effect with the trial data available however considered it was reasonable to assume that riociguat was well tolerated and long-term treatment is possible with some potential benefits to survival.

12.36. The Committee considered the currently used treatments in New Zealand are used off label and there is a lack of head-to-head trials for riociguat in comparison to these treatments. However, it is unlikely this data will be generated.

Suitability

12.37. The Committee considered that the currently funded treatments were administered two to three times a day, and therefore riociguat would not represent an additional treatment burden to the individual. The Committee further considered that riociguat treatment may reduce the frequency of liver function tests and therefore reduce the additional travel and clinic time for the individual for blood testing.

12.38. The Committee considered that a single agent treatment may improve adherence to treatment compared to combination therapy. The Committee considered this was especially true for individuals with comorbidities, that require more complex management.

Cost and savings

12.39. The Committee considered the potential population may be larger than estimated, as there is no formal process to refer individuals to the Auckland clinic if they present with breathlessness.

12.40. The Committee considered the potential survival benefits of riociguat treatment are unclear.

12.41. The Committee considered that the introduction of BPA to New Zealand would not reduce the number of individuals who would receive riociguat. The Committee considered riociguat may be used for short term pre-surgery to reduce pulmonary blood vessel pressures to enable surgery.

Funding criteria

12.42. The Committee considered it would be appropriate to restrict requests for riociguat treatment to being from the national clinic in Auckland.

12.43. The Committee considered that whilst individuals may not improve from riociguat treatment it is reasonable to consider renewal of treatment based on a lack of deterioration.

Summary for assessment

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

Population	Patients with chronic thromboembolic pulmonary hypertension (CTEPH) which is persistent following ballon pulmonary angioplasty treatment or pulmonary endarterectomy (PEA) or is inoperable.
Intervention	Riociguat monotherapy: • Starting dose of 1mg tds fortnightly titration to a maximum dose of 2.5mg tds
Comparator(s)	Standard of care treatment with: • Bosentan (125 mg twice daily) • Sildenafil (50mg three times daily)
Outcome(s)	Based on the Ghofrani et al. 2013 • Improvement in 6 minutes working distance • Improvement in quality of life Based on Held et al. 2025 • Survival benefit is uncertain • Reduction in the frequency of liver testing
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.	

13. Duloxetine – open listing

Application

13.1. The Committee reviewed the clinician application for the listing of generic duloxetine for the management of neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.

13.2. The Committee noted that Pharmac sought advice to support consideration of an open listing for duloxetine, including:

13.2.1. Whether and how duloxetine might be used for major depressive disorder (MDD), generalised anxiety disorder (GAD), and any other indications

13.2.2. Whether duloxetine would provide additional health benefits for these indications versus currently available treatment(s).

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

Recommendation

13.4. The Committee **recommended** that duloxetine be funded (open listed) only if **cost-neutral to venlafaxine**.

13.5. In making this recommendation, the Committee considered:

13.5.1. The likely similar level of benefit duloxetine will provide compared to venlafaxine for people with neuropathic pain, fibromyalgia, chronic musculoskeletal pain, MDD or GAD, while acknowledging uncertainty due to the absence of direct comparative evidence.

13.5.2. The value of having an alternative treatment option alongside venlafaxine.

13.5.3. That there is unlikely to be further evidence from head-to-head randomised clinical trials of duloxetine for these indications.

Discussion

Māori impact

13.6. The Committee noted that the impact of pain on Māori varies depending on the specific indication associated with pain but can be significant where there is disproportionate impact of the condition (eg gout affecting 2.7% in the population but more than 25% of elderly Māori males; Winnard et al. Rheumatology (Oxford). 2012;51:901-9). The Committee noted that anxiety is associated with Māori ethnicity (Lee et al. N Z Med J. 2017;130:10-20), among other risk factors. The Committee noted that there may be higher rates of incontinence in Māori based on risk factors including age and parity (Lara and Nacey. N Z Med J. 1994;107:374-6) and considered that rest home care and obesity are also factors. Members considered that Māori experience similar rates of chronic pain to the general population but experience barriers leading to reduced access to treatment and experience higher rates of disability at the time of presenting for treatment.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

13.7. The Committee noted that there is a strong association between disability and depression in particular resulting in a significant impact for affected individuals (Lillis. S. J Prim Health Care. 2025 Jun 18).

13.8. The Committee noted that the impact of pain on Māori and Pacific people varies depending on the specific indication associated with pain and can be substantial where there is disproportionate impact of the condition. The Committee noted that gout affects 2.7% in the population but more than 25% of elderly Māori and Pacific males, and the incidence of diabetic peripheral neuropathy is three times higher for Māori and Pacific people compared with non-Māori and non-Pacific people). Members considered that, like Māori, Pacific people experience barriers leading to reduced access to treatment.

13.9. The Committee noted that anxiety is strongly associated with increased deprivation, low income, Māori and Pacific ethnicities, depression, and other health comorbidities (Lee et al. N Z Med J. 2017;130:10-20).

Background

13.10. The Committee noted that duloxetine (Cymbalta) is a serotonin-norepinephrine reuptake inhibitor (SNRI) which is now off patent and generic forms are available. The Committee noted that duloxetine is available in New Zealand as 30mg and 60mg capsules; 20 mg and 40 mg forms available internationally and used in clinical trials for stress urinary incontinence (SUI).

13.11. The Committee noted the New Zealand Formulary listed indications for duloxetine are neuropathic pain (part of chronic/persistent pain and its subtypes), Major Depressive Disorder (MDD), and Generalised Anxiety Disorder (GAD). The Committee considered that these were the major indications where duloxetine might be used if open listed and considered each of these in sequence.

13.12. The Committee also considered potential use of duloxetine for stress urinary incontinence (SUI) given there are minimal pharmacological interventions available for SUI in New Zealand and considered that this may result in interest in its use for this indication irrespective of the capsule dose strengths funded.

13.13. The Committee noted that Pharmac approved six Named Patient Pharmaceutical Assessment (NPPA) applications from 2012 to 2026 for duloxetine for individuals with neuropathic pain, depression, and anxiety who met the principles of the NPPA policy.

Depression (Major Depressive Disorder – MDD)

13.14. The Committee noted that there is a 15.3% lifetime prevalence of depression in New Zealand and it is strongly association with female gender, adolescence and young adulthood, increased deprivation, low income, Māori and Pacific ethnicities, disabilities, and other health comorbidities including anxiety disorders (Lee et al. N Z Med J. 2017;130:10-20). The Committee considered that depression is related to significant distress and impairment in important areas of functioning.

13.15. The Committee noted that pharmacological treatments for major depressive disorder (MDD) are second-line to non-pharmacological treatments:

13.15.1. First pharmacological line treatment is an SSRI (eg citalopram, escitalopram, fluoxetine, paroxetine, sertraline) or mirtazapine

13.15.2. Second-line (following an inadequate response to a first SSRI) is a second SSRI, mirtazapine or venlafaxine

13.15.3. Third-line options include tricyclic antidepressants (TCAs), off-label bupropion, or moclobemide

13.15.4. Treatment-resistant MDD may require combination therapy (eg venlafaxine or an SSRI plus mirtazapine); augmentation (eg with lithium or thyroxine); electroconvulsive therapy (ECT); or monoamine oxidase inhibitors (MAOIs).

13.16. The Committee noted that Pharmac has previously considered duloxetine hydrochloride (Cymbalta) for treatment-resistant major depressive disorder (link to Application tracker) as follows:

13.16.1. In July 2008, PTAC deferred making a recommendation pending review by the Mental Health Subcommittee and receipt of further information from the supplier regarding the efficacy of duloxetine in patients who had received suboptimal benefit from previous treatments (link to July 2008 PTAC minutes).

13.16.2. In July 2009, the Mental Health Subcommittee recommended it be funded only if cost neutral and noted that the supplier has subsequently advised that no such data are available (link to July 2009 Mental Health Subcommittee minutes).

13.16.3. Pharmac was unable to achieve cost-neutral pricing. The funding application was declined in 2021 (link to March 2021 decision), based on PTAC's cost-neutral recommendation and clinical advice highlighting possible alternatives.

13.16.4. In February 2022, the Mental Health Advisory Committee considered that the previous cost neutral recommendation remained appropriate and considered that if the range of antidepressants available in New Zealand were to decrease, reconsideration should be given to this medicine (link to February 2022 Mental Health Advisory Committee record).

13.17. The Committee noted that for depression, duloxetine has been recommended by the PBAC in Australia (cost-minimised compared with venlafaxine) and by the SMC in Scotland (restricted to use where resistant to or intolerant of other treatment options), while England/Wales funded a generic duloxetine which is recommended as a third-line treatment. The Committee noted that in Canada, it was considered there was insufficient

evidence of duloxetine having an advantage over SSRIs or as a second-line treatment for depression.

13.18. The Committee noted the broad evidence base for the efficacy, safety, and tolerability of duloxetine in both short- and long-term treatment for MDD, including evidence from a systematic review (Gartlehner et al. Drug Saf. 2009;32(12):1159-73), Cochrane review and meta-analysis (Cipriani et al. Cochrane Database Syst Rev. 2012 Oct 17;10(10):CD00653), and network meta-analysis (Cipriani et al. Lancet. 2018;391:1357-66).

13.18.1. The Committee considered that the 2018 meta-analysis by Cipriani et al was the largest and most methodologically rigorous comparison of antidepressants (including a wide range of newer, second- and third-generation antidepressants, and including a number of head-to-head clinical trials). The authors concluded that duloxetine did not show any advantages over other antidepressants and was less well tolerated than SSRIs and venlafaxine (OR 1.53, 95% CI 1.10–2.13 and OR 1.79, 95% CI 1.16–2.78, respectively). However, the Committee noted that the meta-analyses reported higher rates of discontinuation and side effects with venlafaxine compared with duloxetine.

13.18.2. The Committee noted that Cipriani et al. (2018) reported good evidence of efficacy of duloxetine in acute adult MDD, particularly at higher doses of 80-120 mg/day and the response was dose dependent. The Committee considered that the number needed to treat (NNT) in depression for response was quite good at approximately 4.8 and noted that the NNT for remission was approximately 5.9 versus placebo.

13.19. The Committee noted a range of doses of duloxetine are used in the treatment of depression, but the standard dose is likely to be 60 mg daily.

Anxiety (Generalised Anxiety Disorder – GAD)

13.20. The Committee noted that there is a 15% prevalence of anxiety in adults in New Zealand and a 25% prevalence over a lifetime. The Committee noted that anxiety is strongly association with female gender, adolescence and young adulthood, increased deprivation, low income, Māori and Pacific ethnicities, depression, and other health comorbidities (Lillis. S. J Prim Health Care. 2025 Jun 18).

13.21. The Committee noted that anxiety causes significant distress and/or impairment in important areas of functioning (Ministry of Health New Zealand. 2026. Health and Independence Report 2025 – Te Pūrongo mō te Hauora me te Tū Motuhake 2025. Wellington: Ministry of Health) and is associated with a significant health need.

13.22. The Committee noted that for anxiety/GAD, pharmacotherapy is not used first line but may be appropriate when psychological and behavioural interventions have been ineffective, are unavailable or have been declined. The Committee noted that in New Zealand, pharmacotherapy for GAD is typically approached as follows (BPAC, December 2024):

13.22.1. First line: SSRI or venlafaxine

13.22.2. Second line: alternative SSRI or venlafaxine

13.22.3. Third line: mirtazapine, bupropion, tricyclics, prazosin for post-traumatic stress disorder (PTSD; all unapproved indications) or buspirone, moclobemide for social anxiety disorder (SAD)

13.22.4. Fourth line: pregabalin, antipsychotics, beta blockers (all unapproved indications) or benzodiazepines

13.23. The Committee noted that Pharmac has not previously considered duloxetine for anxiety.

13.24. The Committee noted that for anxiety, duloxetine has been recommended by the PBAC in Australia (cost-minimised compared with venlafaxine) and by the SMC in Scotland (restricted to specialist only), while England/Wales funded a generic duloxetine which is recommended as a second- or third-line pharmacological treatment. The Committee noted that in Canada, it was considered there was insufficient evidence of duloxetine having an advantage over SSRIs or as a second- or third-line treatment for anxiety, however, it has been funded in some states as a second line option.

13.24.1. The Committee noted that in many instances, clinical trials and guidance for anxiety disorders also include other anxiety and related disorders such as panic disorder, obsessive-compulsive disorder (OCD), PTSD, and SAD.

13.25. The Committee noted the evidence base for the efficacy and tolerability of duloxetine for GAD, including evidence from the meta-analyses by Russell et al. (Depress Anxiety. 2008;25(7):E1-11) and Li et al. (PLoS One. 2018 Mar 20;13(3):e0194501). The Committee considered the evidence base was smaller than that for depression and the studies were of good quality.

13.25.1. The Committee noted that the meta-analysis by Russell et al. concluded that there was significantly greater improvement compared with placebo on anxiety symptoms, patient functioning, and on all visual analogue score (VAS) pain items, based on two randomised controlled trials (RCTs) including 798 people with pain and GAD.

13.25.2. The Committee noted the meta-analysis by Li et al. concluded that mean changes in anxiety scores were significantly greater in patients with GAD receiving duloxetine compared to placebo, with meaningful reductions in both psychic and somatic anxiety subscales on the Hamilton Anxiety Rating Scale (HAM-A), based on meta-analysis of eight RCTs. The Committee considered these reductions would be clinically meaningful.

13.26. The Committee considered that for anxiety, a lower dose of 30 mg duloxetine may be used.

Chronic/persistent pain (and its subtypes)

13.27. The Committee noted that almost 30% of the New Zealand population experience chronic pain and there is substantial crossover with other diagnoses of primary pain disorders, neuropathic pain syndromes and nociceptive pain conditions (Borchgrevink et al. J Pain. 2022;23:337-48; van Hecke et al. Pain. 2014;155:654-62). The Committee noted that chronic pain leads to high rates of disability in social, occupational, and quality of life realms; high direct (health) and indirect costs, and impaired global functioning; and is associated with high rates of depression, anxiety, suicide and adverse drug effects (Moore and Davies, Sapere Research Group. 2018).

13.28. The Committee noted that the impact of pain on Māori and Pacific people varies depending on the specific indication associated with pain but can be substantial where there is disproportionate impact of the condition. The Committee noted that gout affects 2.7% in the population but more than 25% of elderly Māori and Pacific males, and the incidence of diabetic peripheral neuropathy is three times higher for Māori and Pacific people compared with non-Māori and non-Pacific people; Winnard et al. Rheumatology (Oxford). 2012;51:901-9)

13.29. The Committee noted that first-line treatment of pain may involve non-pharmacological approaches eg exercise, physiotherapy, psychological therapies, multidisciplinary pain management. The Committee noted that the type of pain should guide pharmacological treatment choice (BPAC, 2021; FPM PS01 [PM], 2025). Members considered there are

currently very few evidence-based treatments for fibromyalgia and that many with neuropathic pain discontinue treatments after some time due to insufficient benefit and/or side effects. The Committee noted that in New Zealand, pharmacotherapy for pain is typically approached according to the type of pain:

13.29.1. Neuropathic pain - First line: TCA's amitriptyline and nortriptyline (unapproved indication) and gabapentinoids pregabalin and gabapentin, carbamazepine for trigeminal neuralgia. Second line – capsaicin, venlafaxine (unapproved indication)

13.29.2. Musculoskeletal (nociceptive) pain - First line: paracetamol, non-steroidal anti-inflammatories (NSAIDs). Second line: capsaicin, TCAs (unapproved indication)

13.29.3. Primary (nociplastic) pain (including Fibromyalgia) - None recommended; TCA's, gabapentin, pregabalin and venlafaxine may be used off label

13.29.4. Migraine prophylaxis: topiramate

13.30. The Committee noted that Pharmac has previously considered the SNRIs duloxetine and venlafaxine for pain (link to Application Tracker).

13.30.1. In July 2013, the Mental Health Subcommittee reviewed SNRIs for neuropathic pain in 2013 and recommended duloxetine be listed for pain with a medium priority based on good evidence of efficacy (particularly in diabetic neuropathy), but noted that venlafaxine likely provides similar benefit despite weaker evidence (link to July 2013 Mental Health Subcommittee minutes). In November 2013, PTAC noted and accepted the Subcommittee minutes (link to November 2013 PTAC minutes).

13.30.2. The Committee noted that Pharmac sought advice in 2025 from both the Mental Health Advisory Committee and the Analgesic Advisory Committee on alternative treatments Pharmac should consider if unable to secure an alternative brand of nortriptyline to manage a supplier discontinuation of that medicine. At that time, both Committees considered that duloxetine would be a beneficial treatment option to have for depression and pain.

13.31. The Committee noted that Pharmac had recently received a clinician application for duloxetine (generic) for neuropathic pain / fibromyalgia / chronic musculoskeletal pain.

13.32. The Committee noted that for chronic pain, duloxetine has been recommended by the SMC in Scotland (restricted to prescribers experienced in the management of diabetic peripheral neuropathic pain as second- or third-line therapy). The Committee noted that the NICE clinical guidelines for England/Wales describe duloxetine as a first-line pharmacological treatment option for neuropathic pain (except trigeminal neuralgia) and that it could be considered for some off-label pain indications eg chronic primary pain. The Committee considered that duloxetine had been recommended and funded for pain in Canada, although documentation of this consideration was not identified.

13.33. The Committee noted the extensive evidence base for duloxetine for pain indications including the following:

- Lunn et al. Cochrane Database Syst Rev. 2014 Jan 3;2014(1):CD007115.
- Ma et al. BMC Musculoskelet Disord. 2023;24:394
- Aleid et al. Brain Behav. 2025;15:e70217
- Birkinshaw et al. Cochrane Database Syst Rv. 2023 May 10;5(5):CD014682

- Moore et al. Rheumatology (Oxford). 2025 May 1;64(5):2385-2394
- Farag et al. JAMA Network Open. 2022;5(5):e2212939.
- Migliorini et al. J Orthop Surg Res. 2023 Jul 17;18(1):504
- Hirase et al. Cureus. 2021 May 22;13(5):e15169.
- Bafail et al. Exp Ther Med. 2024; 28: 448

13.34. The Committee considered the evidence included good quality reviews and meta-analyses supporting a benefit from duloxetine for reducing chronic pain across indications including diabetic peripheral neuropathy, fibromyalgia and chronic musculoskeletal pain. However, the Committee noted that there was little evidence beyond six months of treatment.

13.34.1. The Committee noted Alied et al. investigated the use of duloxetine post-spinal surgery and considered this an example of additional indications where access to duloxetine might be sought if it were funded without restriction.

13.34.2. The Committee noted the evidence from Birkinshaw et al. (2023) indicated a consistent signal of benefit in chronic pain with a standard dose of 60-80 mg duloxetine and considered it moderately efficacious across all outcomes at this dose.

13.35. Members considered that, in the context of neuropathic pain, venlafaxine and duloxetine are both likely to be prescribed in combination with gabapentin/pregabalin for some patients. Members noted there was an absence of data to indicate any difference in how likely each is to be co-prescribed with gabapentin/pregabalin, although considered there are unlikely to be differences.

13.36. Members considered that duloxetine would be expected to be prescribed for people with nociplastic pain and central sensitisation given that this is known to already occur off-label with venlafaxine.

Stress Urinary Incontinence (SUI)

13.37. The Committee considered that stress urinary incontinence is highly relevant to women during the pre- and perimenopausal years. The Committee noted that 43.5% of women aged 16-74 in New Zealand report incontinence occurring daily or weekly (Weatherall et al. N Z Med J. 2024;137:59-72) and that SUI makes up approximately half of all incontinence (Moller et al. Acta Obstet Gynecol Scand. 2000;79:298-305). Members noted there may be higher rates of incontinence in Māori based on risk factors including age and parity (Lara and Nacey. N Z Med J. 1994;107:374-6) and considered that rest home care and obesity are also factors.

13.38. The Committee noted that treatments for SUI are predominantly pelvic floor muscle training (PFMT) and surgical interventions, whilst in New Zealand, there are no effective pharmacological interventions available for SUI. The Committee noted that surgical interventions can be very efficacious in cases of severe incontinence, but that this is not readily available to patients. The Committee noted that access to PFMT is also highly variable, especially in rural and socioeconomically disadvantaged regions. The Committee considered it likely that any newly funded pharmacological options could be strongly preferred to surgery given past health issues with the use of surgical mesh in pelvic slings in New Zealand, despite surgical approaches without mesh being potential options for some. In addition, there are currently limited pharmacological treatment options for people who do not qualify for surgery.

13.39. The Committee noted that Pharmac has not previously considered duloxetine for SUI.

13.40. The Committee noted duloxetine is funded for SUI in the European Union and Scotland (restricted to severe SUI in addition to pelvic muscle floor training). The Committee noted the NICE guidelines (England/Wales) state that duloxetine may be offered as second-line therapy for women who prefer pharmacological to surgical treatment or are not suitable for surgical treatment.

13.41. The Committee noted several systematic reviews and meta-analyses (Maund et al. CMAJ. 2017;189:E194-E203; Mangir et al J Urol Surg 2023;10:1-8; Li et al Int Urol Nephrol. 2013;45:679-86). The Committee noted these reported statistically significant but modest efficacy in the treatment of SUI (incontinence episode frequency; IEF) with number needed to treat (NNT) for a Patient Global Impression of Improvement rating of "much better or very much better" was 8 which was limited by side effects, noting the number needed to harm (NNH) was 7 for discontinuation because of an adverse event. Members noted that the benefit to harm balance was therefore quite marginal, and therefore the number of people who would remain on treatment in the long term was uncertain. The Committee noted the duloxetine discontinuation rates reported for SUI were greater than in other indications and considered duloxetine may provide a modest benefit in the treatment of SUI, but use will be affected by the side effect profile.

13.42. The Committee noted the 20 mg and 40 mg forms of duloxetine available internationally were used in clinical trials for stress urinary incontinence (SUI).

13.43. The Committee considered that high interest in accessing duloxetine for SUI would be expected if duloxetine were funded due to the high health need in SUI; the clear, modest efficacy of duloxetine in this setting; and the lack of other pharmacological treatments available for SUI meaning that individuals are either managing without treatment or may not have presented for treatment at all.

13.44. Members considered that duloxetine might be sought for use after PFMT alone, in combination with PFMT, and possibly prior to surgical interventions. The Committee considered it unlikely that duloxetine would displace surgery for SUI to any meaningful extent, if funded.

13.45. Members considered that if duloxetine were funded without restriction, it would be optimal to fund the dose strengths relevant to treatment of SUI to limit the possibility of incorrect doses being used off label, given the lack of alternative treatments for this indication.

General

13.46. The Committee considered the evidence indicated that duloxetine:

13.46.1. Is generally non-inferior to other medicines for neuropathic pain, fibromyalgia, chronic musculoskeletal pain, MDD and GAD. However, the Committee noted that it is possible that duloxetine is inferior to venlafaxine for depression (though as efficacious as most SSRIs), and superior to venlafaxine for neuropathic pain.

13.46.2. Has advantages and disadvantages compared with venlafaxine in settings where it is the most relevant comparator, with a broadly similar efficacy and side effect profile. However, members noted that the side effect profile of duloxetine increases significantly beyond a 90 mg dose (eg in SUI trials including 80 mg doses which report high discontinuation rates due to intolerance) and members considered this would be a barrier to its use in indications requiring higher doses.

13.46.3. Requires less complex titration than some comparators (eg venlafaxine, gabapentinoids), and similar titration to others (SSRIs, TCAs for pain).

13.47. The Committee considered the evidence for duloxetine was generalisable to the New Zealand context and that limitations of the evidence included the lack of long-term safety

or efficacy data for all indications considered and limited evidence for people with both chronic pain and depression (a common clinical presentation for the New Zealand population).

13.48. The Committee considered it unlikely that any further head-to-head clinical trials would be conducted in future for any indications, given that the patent for duloxetine has expired.

13.49. Members considered that funding an alternative treatment option for these indications where there are few treatment options available would provide benefit for individuals living with these chronic conditions, and that having more treatment options would be positively received by clinicians

13.50. The Committee considered that there could be substantial use of duloxetine beyond the specific indications considered, including SUI and specific short- or long-term uses in oncology (eg to manage symptoms relating to side effects of chemotherapy or hormonal treatments).

Cost and savings

13.51. The Committee considered duloxetine is unlikely to be used as a first-line treatment for any indication, and may instead be used as an alternative option in a similar position to the currently funded SNRI, venlafaxine, for MDD, GAD and pain. The Committee considered that duloxetine's place in SUI therapy is less certain as venlafaxine is not used in this setting and the availability of effective treatment options is limited in New Zealand.

13.52. The Committee considered that estimating the proportions and numbers of people who might use duloxetine for each indication, if funded without restriction, was highly uncertain given the clinical overlap between indications and noting the international funding, approvals and guidelines for differing groups or places in therapy (eg before or after use of venlafaxine depending on indication). However, members considered that:

13.52.1. The greatest proportion of use would be expected to occur in depression, followed by pain, followed by anxiety. There is considerable uncertainty regarding the proportion of people who may receive duloxetine for SUI, and what the relative size of this population will be compared with other indications.

13.52.2. Within pain, the greatest proportion of use would be expected to occur in neuropathic pain, followed by fibromyalgia (given the limited evidence-based treatments and expected interest to try a newly funded treatment with efficacy reported in other indications), followed by musculoskeletal pain. However, over time, the higher proportion of individuals trialing duloxetine may be those with fibromyalgia, followed by neuropathic pain, followed by other primary pain disorders and musculoskeletal pain.

13.52.3. In chronic pain with depression, duloxetine is likely to be favoured due to simpler dosing (venlafaxine requiring higher doses to be effective for chronic pain) and guidelines support a preference for duloxetine if pain is more disabling, but venlafaxine may still be favoured if depression is severe.

13.52.4. For patients with anxiety symptoms and comorbid chronic pain, guidelines generally suggest duloxetine be considered as an option.

13.52.5. Evidence from real-world settings may be more relevant for Pharmac assessment of usage patterns than clinical trial data for duloxetine.

13.53. Members considered that in clinical practice and especially general practice, there is substantial cross-over between groups who might be considered for duloxetine (eg

chronic pain and anxiety, or chronic pain and depression) which could impact on the dose selected for particular individuals.

13.54. The Committee noted that substantial increases in prescribing of duloxetine have occurred in some jurisdictions (eg USA and UK) following funding, with increases of greater magnitude than those seen for other antidepressants. Members considered that the driver of this was unclear but noted it may reflect duloxetine's use in pain and other indications. The Committee also noted that prescribing rates for funded treatments for pain, anxiety and MDD in New Zealand have increased in recent years, but it is uncertain whether, and to what extent, funding duloxetine would affect current prescribing projections.

13.55. The Committee considered that uptake of duloxetine may be high across all indications among people who are not well managed on current treatments, with potentially greater uptake in those with chronic pain given the limited availability of evidence-based and effective options. Members considered that open-listing duloxetine would largely displace existing treatments for the majority of people in these indications, primarily venlafaxine usage, rather than provide treatment for people currently not utilising another pain modulating medication.

13.56. The Committee considered that open-listing duloxetine may initially increase the total number of people receiving treatment for the relevant indications, where people trial a newly funded option without displacing any current treatment (eg for SUI and for other indications where no active treatment is being received); the appropriate comparator for these individuals would be no funded treatment. The Committee considered that the benefits for people where duloxetine is not displacing current treatment are uncertain; therefore, any increase in the overall population may be short-lived, reflecting use of a therapy with similar benefits to existing options. Members considered that the relative contribution of these people to the total eligible population is uncertain and that a small, unknown proportion of people who switch to duloxetine may later prefer to return to their previous treatment or to no pharmacological treatment.

Summary for assessment

13.57. The Committee considered that the most appropriate comparator for an assessment of open-listing duloxetine is venlafaxine. Members considered that a standard duloxetine dose of 60 mg per day could be compared with 150 mg per day of venlafaxine for the purposes of the analysis. This approach is consistent with the equi-effective doses used in the PBAC assessment for MDD, the indication in which duloxetine is expected to be most widely used, and for chronic pain, where venlafaxine 150mg per day is the minimally effective dose. The Committee considered duloxetine could provide an improved level of benefit compared to venlafaxine for people with neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, and a similar level of benefit compared with venlafaxine in MDD or GAD, while acknowledging uncertainty due to the absence of direct comparative evidence. Members considered that prescribing data for venlafaxine could be used to estimate potential use in this population.

13.58. The Committee reiterated that for some people, duloxetine may be trialed if it were funded without displacing any current treatment and that the most appropriate comparator for these people would be no treatment.

14. Anacaulase-bcdb for thermal burns, deep partial/ full thickness, eschar removal

Application

14.1. The Committee reviewed the application the use of anacaulase-bcdb (Nexobrid) for eschar removal of deep partial/full thickness thermal burns.

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

Recommendation

14.3. The Committee **recommended** that anacaulase-bcdb for people with thermal burns (deep partial/full thickness) for eschar removal be listed with a **high priority**, subject to the following Special Authority criteria:

> **Initial application – (deep partial or full thickness thermal burns)** only from a relevant specialist or any other practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Treatment is to be administered within the National Burns Service by healthcare professionals trained in its use, under the direction of a burns surgeon

14.4. In making this recommendation, the Committee considered the following:

14.4.1. A high unmet health need, given the severity, complexity, and long-term impacts of deep partial- and full-thickness burns, and limitations of current surgical management.

14.4.2. Clinically meaningful benefits, particularly the substantial reduction in need for surgical excision, supported by consistent evidence across trials, with additional benefits including reduced blood loss and faster eschar removal.

14.4.3. Potential to reduce pressure on constrained health system resources, including operating theatre utilisation, anaesthesia requirements, and blood product use, with implications for wider system efficiency.

Discussion

Impact on Māori, Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

14.5. The Committee noted evidence of ethnic and socioeconomic inequities in burn injury (Mistry, et al. Burns. 2010;36(3):403-8), with Māori and Pacific peoples experiencing a higher burden of burns requiring hospitalisation, and Māori and Pacific children reported to be approximately three times more likely to be hospitalised for burn injury compared with New Zealand (NZ) European children (Safekids Aotearoa, 2020).

14.5.1. The Committee further noted that differences are observed in management, with Māori more likely to undergo surgical wound procedures and slightly less likely to receive skin grafting compared with the overall population (2021-2022 BRANZ).

14.6. The Committee noted that other groups experiencing health inequity, including those in rural communities and areas of high socioeconomic deprivation, may face barriers to accessing specialist burns care, including delays in treatment, increased travel burden, and separation from whānau when care is centralised.

14.7. The Committee noted that burn injuries have substantial impacts on family and whānau who often provide wound care, psychosocial support (Bäckström et al.J burnso.2018;2;

193-8), as well as assistance with recovery, and may experience reduced quality of life (Hsu et al. Burns. 2023;49(2):317-28), role changes and psychological distress including symptoms consistent with post-traumatic stress with these burdens (Patterson et al. Burns. 2023;49:1311-20) potentially exacerbated in the New Zealand context due to travel and separation from home when care is provided at specialist burns centres.

Background

14.8. The Committee noted that funding has previously been provided for supportive treatments for burns, including multivitamin and mineral supplementation in the hospital setting since 2015 and selenium and copper chloride since 2022, while other treatments such as leptospermum (manuka honey) have been considered but not funded.

Health need

14.9. The Committee noted that burn injuries vary widely in depth, extent, and cause, ranging from superficial injuries with relatively rapid recovery to deep partial- and full-thickness burns that may require prolonged healing, surgical intervention, and are associated with a high risk of scarring, systemic complications, and multi-organ effects. The Committee further noted that more severe burns, particularly those involving larger total body surface areas, can result in significant physiological stress, including burn shock and increased risk of infection, and are associated with substantial and persistent impacts on function, pain, psychological wellbeing, and health-related quality of life (HRQoL) in both adults and children.

14.10. The Committee was made aware of evidence from the Burns Registry of Australia and New Zealand (BRANZ) long-term outcomes study (Tracy, et al. Burns Trauma. 2020;8:tkz004) indicating that itch affected approximately 50% of adults at one month and 27% at 12 months, while moderate-to-severe pain decreased over time but remained present, and that pain was associated with a greater negative impact on quality of life and work outcomes than itch.

14.11. The Committee noted that, while current standard of care for burn debridement is generally effective, there remains an unmet health need due to limitations of surgical excision, including the risk of over-excision of viable tissue and increased blood loss.

Health benefit

14.12. The Committee noted that anacaulase-bcdb is a topical enzymatic debridement treatment used for the removal of eschar in acute deep partial-thickness and full-thickness thermal burns.

14.12.1. The Committee noted that the treatment contains a mixture of proteolytic enzymes derived from bromelain, which selectively digest non-viable burn eschar while preserving viable dermal tissue.

14.13. The Committee noted that the anticipated clinical benefits include faster eschar removal, reduced need for surgical excision, reduced procedure-related blood loss, and a potential reduction in the need for skin grafting where viable dermis is preserved.

14.14. The Committee noted the DETECT trial (Shoham et al. J Burn Care Res. 2024 ;45:297-307), a phase 3, multicentre, assessor-blinded randomised controlled trial conducted across multiple international burn centres, which compared anacaulase-bcdb with standard of care and placebo in adults with deep partial or full thickness burns, involving between 3% and 30% of their total body surface area (TBSA).

14.14.1. The Committee noted that the mean TBSA per person (all wounds) ranged from 8.3% to 9.0% across treatment groups, which may be lower than the

TBSA typically seen in patients treated at the National Burns Centre, which generally manages patients with burns exceeding 10% TBSA.

14.14.2. The Committee noted that a greater proportion of patients treated with anacaulase-bcdb achieved complete eschar removal compared with placebo gel vehicle (93% vs 4%; P<0.001).

14.14.3. The Committee noted that treatment was associated with a reduced need for surgical excision compared with standard of care (4% vs 72%; P<0.001).

14.14.4. The Committee noted that anacaulase-bcdb reduced the time to complete eschar removal compared with standard of care (median 1.0 vs 3.8 days; P<0.001).

14.14.5. The Committee noted that anacaulase-bcdb was associated with reduced blood loss during eschar removal compared with standard of care (mean 14 mL vs 814 mL; P<0.0001).

14.14.6. The Committee noted that scar outcomes, measured by the Modified Vancouver Scar Scale (MVSS), were reported to be non-inferior between anacaulase-bcdb and standard of care at 12 and 24 months.

14.14.7. The Committee noted that treatment with anacaulase-bcdb reduced the need for general anaesthesia compared with surgical excision and was not associated with an increase in serious adverse events.

14.14.8. The Committee noted that serious adverse events occurred across treatment groups, with no clear treatment-related long-term safety signals or treatment-related adverse events identified beyond 12 months.

14.15. The Committee noted that, in an open label randomised controlled trial of anacaulase-bcdb in children with deep partial- and full-thickness burns (covering 1% to 30% of TBSA), treatment was associated with faster time to eschar removal compared with standard of care (median 1 vs 6 days; P<0.001) and a substantially lower proportion of wound area requiring surgical excision (mean 1.5% vs 48.1%; P<0.001) (Shoham et al. Burns 2025;51:107417).

14.15.1. The Committee noted that anacaulase-bcdb was associated with similar long-term scar outcomes compared with standard of care, with non-inferior MVSS scores at 12 months (3.8 ± 2.9 vs 4.9 ± 3.3; P<0.001).

14.15.2. The Committee noted that time to complete wound closure was numerically shorter with anacaulase-bcdb compared with standard of care (median 21 vs 34 days), although overlap in reported ranges limited interpretation of this difference.

14.15.3. The Committee noted that rates of adverse events were similar between treatment arms, with no new safety concerns identified in the paediatric population.

14.16. The Committee noted that, in a multicentre randomised controlled trial in children and adults aged 4–55 years with deep partial- and full-thickness burns, anacaulase-bcdb was associated with a reduction in time from injury to complete eschar removal compared with standard of care (2.2 vs 8.7 days; P<0.0001) and a reduced need for surgical intervention (24.5% vs 70.0%; P<0.0001) (Rosenberg et al. Burns. 2014;40:466-74).

14.16.1. The Committee noted that anacaulase-bcdb reduced the extent of burns requiring excision (13.1% vs 56.7%; P<0.0001) and the need for autografting

(17.9% vs 34.1%; P=0.01), with 6.8% of participants requiring a second application to achieve complete debridement.

14.16.2. The Committee noted that long-term follow-up (2–4 years) demonstrated similar scar outcomes between anacaulase-bcdb and standard of care (mean MVSS 3.12 vs 3.38;P=0.88), with fewer donor site scars reported in the anacaulase-bcdb group.

14.16.3. The Committee noted that the quality of life outcomes were similar between treatment groups, with no new long-term safety concerns identified.

14.16.4. The Committee noted that the study used an open-label design conducted in an earlier adoption setting, which may introduce uncertainty and limit comparability to more recent trials such as DETECT.

14.17. The Committee noted that treatment with anacaulase-bcdb results in faster time to complete eschar removal compared with standard of care, based on evidence from both adults (DETECT) and paediatric trials, but considered that this outcome may be of limited relevance for economic modelling as it does not clearly translate to a reduced length of inpatient stay.

14.17.1. The Committee noted that anacaulase-bcdb is associated with reduced blood loss during eschar removal compared with standard of care, which may represent an additional clinically meaningful benefit.

14.17.2. The Committee noted that, in addition to clinical benefits, avoidance of surgical excision may provide meaningful benefits for patients, whānau, and caregivers, including reduced treatment burden and procedural risk, as well as benefits to clinicians and the wider health system through reduced reliance on surgical resources.

14.18. The Committee noted that the primary clinical value of anacaulase-bcdb is in reducing the need for surgical excision, with modelling best informed by evidence from the DETECT trial in adults and paediatric trial data, and that the magnitude of this benefit is likely to be influenced by implementation quality, with early implementation potentially associated with higher rates of combined enzymatic and surgical debridement due to a learning curve.

14.19. The Committee noted that scenario analyses may be appropriate to reflect uncertainty in implementation, including best-case estimates aligned with DETECT, worst-case estimates based on earlier studies, and intermediate scenarios reflective progressive improvement in outcomes over time with increased clinical experience and training.

14.20. The Committee noted that some evidence suggests a reduction in the need for autografting with anacaulase-bcdb, although this finding is not consistently reported across studies and was not reported in the DETECT trial, despite being included in the study protocol, introducing uncertainty regarding the magnitude of this effect.

14.20.1. The Committee noted that, due to this uncertainty, any potential reduction in autografting may be more appropriately explored through scenario analyses rather than assumed in the base case.

Suitability

14.21. The Committee noted that the clinical benefit of anacaulase-bcdb is dependent on effective implementation, and that if a substantial proportion of patients require both enzymatic and subsequent surgical debridement, the value of the new treatment may be significantly reduced.

14.22. The Committee noted that a structured implementation approach would likely be required to support optimal use of anacaulase-bcdb, including the development of national guidance and centre credentialling, to mitigate variability in practice and support safe and effective adoption.

14.22.1. The Committee noted that there is limited published evidence describing management and anaesthesia requirements associated with anacaulase-bcdb, and that further engagement with burns clinicians, including international experience, may be valuable to understand sedation requirements and potential impacts on operating theatre utilisation to better inform assessment of comparative value.

14.23. The Committee noted that enzymatic debridement has device-like characteristics, including a learning curve associated with wound bed assessment and interpretation of dermal viability, which may initially result in increased use of surgical intervention and resource use.

14.23.1. The Committee noted that early implementation may require higher levels of sedation, use of specialised environments (e.g. procedure rooms or post-anaesthesia care unit), and increased staffing, reflecting the complexity of the procedure during the learning phase.

14.23.2. The Committee noted that with increased experience, enzymatic debridement may become more streamlined, with treatment increasingly delivered bedside under regional anaesthesia and requiring fewer personnel.

14.23.3. The Committee noted that international consensus guidance describes enzymatic debridement as a specialist procedure requiring specific training, infrastructure adaptation, and multidisciplinary involvement and recommends ongoing data collection to monitor outcomes during implementation.

14.23.4. The Committee noted that anacaulase-bcdb requires appropriate pain management before and during administration, similar to that required for extensive dressing changes, and that preparation and handling require precautions to minimise healthcare worker exposure, as well as adherence to cold-chain storage requirements (2–8°C, do not freeze).

14.24. The Committee noted that reduced reliance on surgical excision may improve operating theatre capacity for other urgent cases and may be particularly beneficial during periods of high demand or constrained surgical resources.

Cost and savings

14.25. The Committee noted that implementation of enzymatic debridement would require specific staff training, adaptation of infrastructure and multidisciplinary involvement.

14.26. The Committee noted that enzymatic debridement with anacaulase-bcdb may reduce health system resource use, including operating theatre utilisation, blood products, and clinical workforce requirements, based on expert consensus.

14.27. The Committee noted that surgical management of burns is resource-intensive and may require use of operating theatre capacity, which has associated opportunity costs within the health system, and that the use of anacaulase-bcdb may reduce these demands through fewer surgical eschar removal procedures, reduced theatre time and anaesthesia exposure, and reduced blood loss and transfusion requirements, with any potential reduction in grafting remaining uncertain.

14.28. The Committee noted that implementation is likely to be gradual due to a learning curve and variable clinician adoption, and that modelling should incorporate assumptions regarding increasing uptake over time.

14.29. The Committee noted that the supplier's estimate of eligible patient numbers (128 patients per year) may be inflated by inclusion of patients with non-thermal or otherwise unsuitable burns, and that refinement based on clinical input would be required, with consideration of lower initial uptake and comparator data from other centres to inform more realistic base-case assumptions.

14.30. The Committee considered that a reduction in length of inpatient stay was not supported by the available clinical trial evidence, however this may warrant further investigation and could be explored in the economic model through scenario or sensitivity analyses based on observational data.

Funding criteria

14.31. The Committee noted that the supplier proposed positioning of anacaulase-bcdb as a replacement for standard of care, including surgical excision, is likely overstated, and that its role is more appropriately considered as reducing the need for surgical eschar excision in selected patients with deep partial- and full-thickness thermal burns, while other elements of care, including wound closure and grafting, would still be required.

14.31.1. The Committee further noted that anacaulase-bcdb represents an alternative to initial surgical eschar excision in selected patients, which may enable earlier wound-bed assessment and reduce the extent of perioperative debridement, while introducing a distinct, device-like treatment pathway with different workflows that operate in parallel with, and may transition to, conventional surgical pathways depending on individual treatment response.

14.32. The Committee noted that there may be clinical scenarios where anacaulase-bcdb is not suitable for use, including non-thermal burns and wounds involving sensitive anatomical areas, significant comorbidities, or risk of exposure of critical structures, and that decisions regarding suitability should remain subject to specialist clinical judgement.

14.33. The Committee noted that, given the complexity and variability of burn presentations, treatment with anacaulase-bcdb should be limited to specialist burns centres, with patient selection and contraindications manged through clinical discretion rather than prescriptive access criteria.

14.33.1. The Committee noted that, if anacaulase-bcdb were to be restricted to specialist burns services, implementation would need to include clear and equitable pathways for referral, transfer, assessment, and whānau support to mitigate access barriers.

14.34. The Committee noted that the PICO should be revised to include both adults and children treated in specialist burn centres, with intervention restrictions reflecting regulatory limits on maximum treatment area and administration by trained clinicians, while outcomes should be reframed to capture clinically relevant endpoints including completeness of eschar removal, need for surgery and grafting, scarring, quality of life, complications and health system use.

Summary for assessment

14.35. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for anacaulase-bcdb if it were to be funded in New Zealand for thermal burns, deep partial/full thickness, eschar removal. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff.

This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People (adults and children) hospitalised with deep-partial thickness (DPT) and/or full-thickness (FT) thermal burns, treated within a regional or national burns centre.
Intervention	Enzymatic debridement with anacaulase-bcdb as part of standard inpatient burns management, applied by trained clinicians within a defined burns care pathway. • Maximum of 15% TBSA treated per application • May be repeated (e.g. second application after 24 hours if required • Total treated area generally not exceeding 20% TBSA, consistent with regulatory guidance • Followed by delayed surgical debridement if eschar removal is incomplete after non-surgical methods.
Comparator(s) (NZ context)	Standard of care inpatient management without enzymatic agents, which may include: • Surgical debridement (early tangential excision) • Non-enzymatic conservative debridement (mechanical or autolytic) • Topical management • Followed by delayed surgical debridement if eschar removal is incomplete
Outcome(s)	Clinically relevant outcomes including: • Completeness of eschar removal • Proportion of patients requiring surgical excision • Need for skin grafting and extent of grafting • Scar outcomes at follow-up • Pain, infection rates, and wound complications • Health-related quality of life • Hospital resource use (including length of stay) • Equity of access

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: 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.

15. Risdiplam tablet for Spinal Muscular Atrophy

Application

15.1. The Committee reviewed the application for Risdiplam in the treatment of spinal muscular atrophy (SMA) types 1-3.

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

Recommendation

15.3. The Committee **recommended** that risdiplam 5 mg film-coated tablets for the treatment of spinal muscular atrophy (SMA) types 1-3 be funded if **cost neutral to the funded risdiplam oral solution**, subject to the same access criteria.

15.4. In making this recommendation, the Committee considered:

15.4.1. The bioequivalence of the oral solution and tablets

15.4.2. The suitability aspects of the tablets.

Discussion

Patient lived experience

15.5. The Committee acknowledged a submission providing insights from the SMA community regarding risdiplam oral liquid and tablet formulations. The submission supported having both the oral liquid and tablet formulations available, noting the liquid formulation is needed for young children and/or people with swallowing difficulties.

15.6. The submission described the daily challenges with the oral liquid formulation, including refrigeration requirements, complexity for travel and difficulty training others to store and use the liquid safely.

15.7. The submission noted that the tablet formulation is easier to transport, mitigating many of the current challenges for individuals participating in daily activities. The longer storage life, easier administration and dosing would prevent carer worry regarding treatment and the need for training of others.

15.8. The Committee wished to express their gratitude to the individual for their submission on behalf of the SMA community. The Committee acknowledged the daily challenges individuals have with the current formulation and thanked the individual for providing their lived experience of how the current formulation affected their daily lives.

General

15.9. The Committee noted that Pharmac currently funds risdiplam powder for oral solution (2 g powder for reconstitution into oral solution; 60 mg active ingredient) under Special Authority criteria for Spinal Muscular Atrophy (SMA) types 1-3. The oral solution is reconstituted by a health professional during the dispensing process. The recommended dose is weight-dependent, with a fixed dose of 5 mg per day for people 20 kg and over, and 0.25 mg per kg for those under 20 kg. The Committee noted that the solution requires refrigeration and needs to be administered within 5 minutes of it being drawn up into the dosing syringe.

15.10. The Committee noted that this application is for a new formulation of risdiplam, the 5 mg tablets. These strawberry flavoured tablets are taken once daily, either swallowed as

whole tablet or dispersed in bottled (non-chlorinated) water. The tablets are stable at room temperature for 36 months.

15.11. The Committee considered there is no current unmet health need in this population due to the availability of risdiplam oral solution.

15.12. The Committee reviewed the pivotal phase 1 study (BP42066) and noted that it showed bioequivalence between the tablet and oral solution (whether swallowed whole or dispersed in water).

15.13. The Committee considered that there are suitability advantages with the tablet, including storage flexibility and simpler administration, as described in the patient lived experience submission.

15.14. The Committee noted that Roche New Zealand is responsible for the direct delivery programme for risdiplam oral solution, and that this same arrangement would be used for the delivery of the tablets.

15.15. The Committee considered that the majority of people are likely to switch from the oral solution to the tablets (with the exception of people who require a dose less than 5 mg). The Committee considered there could potentially be an increased uptake in risdiplam for people without adequate access to continuous refrigeration, such as rural populations. However, the Committee noted that direct delivery programme for risdiplam reduces this barrier so the impact is likely to be minimal.

Summary for assessment

15.16. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for risdiplam tablets if it were to be funded in New Zealand for SMA types 1-3. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with SMA types 1-3 who weigh 20 kg or more and are 2 years of age or older who are currently receiving 5 mg daily dose
Intervention	Risdiplam tablet 5 mg
Comparator(s)	Risdiplam oral solution 5 mg
Outcome(s)	Equivalent outcomes between intervention and comparator
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.	

16. Durvalumab for muscle invasive bladder cancer (MIBC), neoadjuvant and adjuvant, first-line (with neoadjuvant chemotherapy)

Application

16.1. The Committee reviewed the application for durvalumab for the first-line treatment of muscle invasive bladder cancer.

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

Recommendation

16.3. The Committee **recommended** widening access to durvalumab with a **high priority** for the first-line neoadjuvant and adjuvant treatment of muscle invasive bladder cancer (MIBC) and subject to the following Special Authority criteria:

Durvalumab
Initial application (muscle invasive bladder cancer – resectable)
Applications only from any relevant practitioner. Approvals valid for 4 months.
All of the following:

1. Individual has resectable urothelial muscle invasive bladder cancer; and
2. Individual has not received prior treatment with systemic therapy for muscle invasive bladder cancer; and
3. Individual has ECOG status of 0-2; and
4. Durvalumab to be administered in combination with platinum-based chemotherapy for up to 4 cycles prior to surgery; and
5. Treatment must be prior to radical cystectomy

Renewal (muscle invasive bladder cancer - resectable)
Applications only from any relevant practitioner. Approvals valid for 4 months.
All of the following

1. Individual has undergone cystectomy; and
2. Individual has received prior durvalumab in combination with platinum-based chemotherapy in the neoadjuvant setting; and
3. No evidence of disease progression; and
4. Initiation of adjuvant therapy is no more than 6 months after surgery with no evidence of disease progression; and
5. Durvalumab monotherapy to be administered every four weeks for up to eight cycles following surgery

16.4. In making this recommendation, the Committee considered:

- The high unmet health need of individuals with muscle invasive bladder cancer
- Durvalumab treatment was associated with clinically meaningful health benefit
- Additional costs and resources for monitoring of patients following treatment with immune checkpoint inhibitors (ICI).

Discussion

Māori impact

16.5. The Committee discussed the impact of funding durvalumab for the treatment of MIBC on Māori health areas of focus and Māori health outcomes.

16.6. The Committee noted MIBC is not a Hauora Arotahi (Pharmac Māori Health Areas of Focus).

16.7. The Committee noted PTACs consideration of urothelial carcinoma in November 2025, and considered that similarly to urothelial carcinoma, while Māori have a similar incidence

of MIBC compared to Europeans, they present with a more advanced stage of disease at the time of presentation.

16.8. The Committee noted bladder cancer is four times more likely in men than women, and Māori men and non-Māori men are diagnosed at a rate of 7.49 and 8.08 per 100,000 respectively compared to female Māori and non-Māori at a rate of 3.9 and 2.37 per 100,000 respectively.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

16.9. The Committee noted PTACs consideration of urothelial carcinoma in November 2025 and considered that, similarly to urothelial carcinoma, Pacific peoples have a lower incidence of MIBC compared to Europeans, however, they present at the clinic at a more advanced stage of disease.

16.10. The Committee noted a 10-20% higher incidence of MIBC in lower socioeconomic groups and considered this was likely due to smoking, which is a risk factor for developing MIBC.

Health need

16.11. The Committee noted that the health need of individuals with urothelial cancer had recently been considered by PTAC in November 2025.

16.12. The Committee considered urothelial cancer is the predominant histological variant, comprising 95% of bladder cancer cancers.

16.13. The Committee considered the health need of individuals and whānau with MIBC may vary from those with advanced or metastatic urothelial cancer. The Committee considered individuals with advanced urothelial cancer may not have undergone radical cystectomy (RC) which greatly affects the quality of life of both the individual and resultant increased carer burden. The Committee considered carer burden would remain for all individuals who undergo a RC, regardless of (neo)adjuvant treatment type (chemotherapy or immunotherapy).

16.14. The Committee noted that patients with MIBC are predominantly older males, with a New Zealand study reporting a male to female ratio of 4:1 and a mean age of 70 years (Wild et al. NZ Med J. 2021).

16.15. The Committee noted 80% of individuals diagnosed with bladder cancer present with haematuria, with other symptoms including dysuria, increased frequency and/or urgency (Powles et al. Ann Oncol. 2022;33:244-58).

16.16. The Committee noted that around 25% of bladder cancer is muscle invasive, with up to 15% of patients have a previous history of non-MIBC (Powles et al. Ann Oncol. 2022). The Committee noted all MIBCs are considered as high grade (Powles et al. Ann Oncol. 2022).

16.17. The Committee considered that individuals with MIBC were referred to a multidisciplinary meeting to determine the best treatment course. The Committee considered individuals who are considered suitable for neoadjuvant chemotherapy are referred to medical oncologists for treatment prior to RC.

16.18. The Committee considered that many individuals would have comorbidities that prevent cisplatin-based chemotherapy, including renal functional impairment. The Committee considered the RC surgery is a complex major surgery that would not be suitable for individuals who are clinically frail.

16.19. The Committee considered that uptake of neoadjuvant chemotherapy remained low, noting a Canterbury based study that reported 11% receiving neoadjuvant treatment, despite only 33% of the population having a renal functional impairment that might prevent treatment with chemotherapy. The Committee noted that the study reported a 5-year survival rate of approximately 50% (Wild et al. 2021). The Committee considered uptake of neoadjuvant chemotherapy may vary nationwide.

16.20. The Committee considered the majority (90%) of individuals receiving neoadjuvant chemotherapy would receive gemcitabine and cisplatin (GC).

16.21. The Committee considered a small proportion (10-20%) of individuals would receive dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) instead of GC in the neoadjuvant setting. The Committee considered these individuals would be typically younger and clinically fitter. The Committee considered that MIBC patients who received ddMVAC as neoadjuvant chemotherapy (NAC) would not exhibit outcomes different to those receiving GC. The Committee noted network meta-analyses, which reported that differences in pCR and OS were not statistically significant between ddMVAC versus GC (Noelle et al. Journal of Clinical Question. 2025).

16.21.1. The Committee considered it would be appropriate to use GC as the only comparator for economic modelling due to the similar health benefit to ddMVAC.

16.22. The Committee considered there would be regional variation in the percentage who receive GC compared to ddMVAC across New Zealand.

16.23. The Committee considered that individuals who were not clinically fit enough to receive cisplatin may receive carboplatin, or would not receive neoadjuvant therapy. The Committee considered carboplatin to be less effective than cisplatin.

16.24. The Committee considered that approximately 90% of those who completed neoadjuvant chemotherapy would undergo a RC.

16.25. The Committee considered there was emerging evidence of other therapeutics for the treatment of MIBC including pembrolizumab in combination with enfortumab vedotin. The Committee considered it would welcome funding applications for other therapies including immune checkpoint inhibitors for the treatment of MIBC.

Health benefit

16.26. The Committee noted the NIAGRA study (Powles et al. N Engl J Med. 2024). A phase 3, open-label, randomised trial in which patients were randomised to durvalumab (n=533) or comparator (GC; n=530) arms.

16.26.1. The Committee noted improved event free survival (EFS) at 24 months in 67.8% (95% CI, 63.6 to 71.7) of the durvalumab arm vs 59.8% (95% CI, 55.4 to 64.0) of the comparator arm (hazard ratio (HR) for progression, recurrence, not undergoing radical cystectomy, or death from any cause, 0.68; 95% CI, 0.56 to 0.82; P<0.001 by stratified log-rank test).

16.26.2. The Committee noted pathological complete response (pCR) occurred in 37.3% (95% CI, 33.2 to 41.6) of the patients in the durvalumab group and in 27.5% (95% CI, 23.8 to 31.6) of those in the comparator group (risk ratio, 1.34; 95% CI, 1.13 to 1.60).

16.26.3. The Committee noted the estimated overall survival (OS) at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the durvalumab group and 75.2% (95% CI, 71.3 to 78.8) in the comparator group (HR for death, 0.75; 95% CI, 0.59 to 0.93; P=0.01).

16.26.4. The Committee noted the adverse event (AE) profile of both treatments were similar.

16.26.5. The Committee noted the majority of individuals included had an ECOG performance score of 0 (approximately 80%) with the remaining 20% being ECOG 1. The Committee noted that all individuals in the trial had received neoadjuvant therapy and most were N0. The Committee noted the average age was younger than the average age of individuals with MIBC in New Zealand. Overall, the Committee considered individuals in the NIAGRA trial to be younger and clinically fitter than individuals in New Zealand with MIBC, which likely contributed to the superior OS observed in the control arm compared with Wild et al. 2021.

16.26.6. The Committee noted that approximately 80% of individuals in the trial had a creatinine clearance of ≥60 ml/min/ 1.73m^2, with the remaining 20% between 40-60. The Committee considered this was below the usual clinical threshold for cisplatin treatment (<60ml/min) based on the Galsky criteria.

16.26.7. Overall, the Committee considered the NIAGRA trial to be a well-conducted phase 3 trial reporting high-quality evidence, which showed clear and statistically significant, and clinically meaningful benefit of durvalumab in the neoadjuvant and adjuvant setting in MIBC.

16.26.8. The Committee considered the comparator in the trial (GC) broadly reflected the currently funded treatments available in New Zealand, whereby around 90% of New Zealand patients would receive GC with younger/fitter patients receiving ddMVAC.

16.26.9. The Committee considered that the magnitude of benefit observed in the intervention arm was similar across PD-L1 expression subgroups (high versus low or none).

16.26.10. The Committee considered that it was currently uncertain if pCR was a surrogate marker for PFS or OS within the treatment of bladder cancers.

16.26.11. The Committee considered it was reasonable to assume the health benefits reported in the NIAGRA trial would be applicable to, and observed in, the New Zealand clinical setting.

16.27. The Committee noted efficacy and outcome analyses from the NIAGRA trial (Galsky et al. JCO. 2025).

16.27.1. The Committee noted that individuals who achieved pCR had better EFS and OS vs non-pCR.

16.27.2. The Committee noted durvalumab derived greater EFS and OS benefit vs comparator arm in both pCR (EFS: HR 0.58; 95% CI, 0.33-1.00; OS: HR 0.72; 95% CI, 0.37-1.43) and non-pCR (EFS: HR 0.77; 95% CI, 0.63-0.95; OS: HR 0.84; 95% CI, 0.66-1.07) groups.

16.28. The Committee considered that treatment of MIBC with durvalumab may result in a 25% reduction in mortality rate at 2 years, as indicated by the NIAGRA trial (Powles et al. N Engl J Med. 2024).

16.29. The Committee did not consider treatment with durvalumab to pose any larger clinically significant risks compared with currently funded treatments.

Suitability

16.30. The Committee considered most individuals would receive up to 12 doses of durvalumab in addition to standard of care chemotherapy. Therefore, this would increase the number of infusions for the individual and increase time away from whānau, paid employment and travel time to and from infusion centres.

16.31. The Committee also considered that neoadjuvant therapy needs to be timed carefully in relation to chemotherapy therapy and surgical scheduling, which can be challenging with the current demand on infusion services.

Cost and savings

16.32. The Committee considered approximately 50 people per year would be eligible for peri-operative durvalumab in New Zealand. This consideration was based on numbers from Auckland, where there were between 25-30 referrals for neoadjuvant chemotherapy, some were rejected due to comorbidities, but around 22-25 were treated of which 90% went on to RC.

16.33. The Committee noted that the median number of durvalumab cycles received in NIAGRA was 12 and that this is higher than the mean of 8.8 cycles. The Committee considered that most individuals would receive 10-12 cycles of durvalumab treatment.

16.34. The Committee considered that based on numbers from Auckland and Christchurch, around 60% of individuals with MIBC in New Zealand receive an RC (around 90 patients per year), which equates to around 16% of all bladder cancer cases.

16.35. The Committee considered that there may be a small increase in the number of MIBC patients suitable for RC with durvalumab treatment, based on data reported in the NIAGRA trial (Powles et al. N Engl J Med. 2024). The Committee considered that the increased uptake of RC, roughly 2-3 people per year nationwide, would not have significant impact on health system workforce or resources.

16.36. The Committee considered that the cost savings reported in global studies are likely higher than would be expected in New Zealand, due to the reduced use of expensive second-line therapies, of which many are not currently funded in New Zealand. The Committee considered overall that patient care costs may be reduced over a lifetime owing to delayed or avoided second line treatments with durvalumab treatment.

16.37. The Committee considered the estimates that an uptake of 70% in year one rising to 85% in year five of listing was reasonable, however, the denominator (number of patients) would likely increase because of the new definition of cisplatin-eligibility.

16.38. The Committee considered that the event and disease-free survival curves in the trial data for durvalumab, and other immune checkpoint inhibitors (ICIs) such as nivolumab, were stable at five years, and therefore considered that the risk of relapse for these individuals was likely to decrease in the long term.

16.39. The Committee considered there would be additional healthcare surveillance and monitoring costs associated with eight months of adjuvant ICI therapy. The Committee considered ICI treatment is associated with chronic toxicity that requires additional clinical monitoring and interventions.

16.39.1. The Committee considered that the mean of 8.8 cycles of durvalumab received in NIAGRA would likely underestimate resource use and a higher number of cycles would be more appropriate for the CUA.

16.40. The Committee considered individuals who progressed following (neo)adjuvant durvalumab treatment, and then subsequent relapse with metastatic urothelial carcinoma

would benefit from treatment with an ICI. The Committee noted Maiorano et al. ESMO Open. 2025 that evaluated the effect of ICI rechallenge in this population of individuals, that reported a health benefit. The Committee considered that the health benefit was greater in those who had received prior ICI therapy in the non-metastatic setting, and if the second ICI was received more than 12 months after the prior ICI exposure.

16.41. The Committee noted a German cost utility analysis, which suggested that the average gain in quality-adjusted life years (QALYs) per patient is 0.21, translating into a gross cost per QALY of NZD $120,000 (Rieger et al. European Journal of Cancer. 2025).

Funding criteria

16.42. The Committee noted that 20% of individuals included in the NIAGRA study would not meet the Galsky criteria for initiation of cisplatin treatment based on creatinine clearance levels. The Committee considered these individuals received similar health benefit in the study to those with a creatinine clearance level of ≥60mL/min and it would be appropriate for these individuals to receive treatment with durvalumab.

16.42.1. The Committee considered this would increase the number of patients who were eligible for treatment by 10-20%. The Committee considered these individuals would likely receive cisplatin if they were considered otherwise clinically fit enough. Alternatively, these individuals would receive carboplatin therapy.

16.42.2. The Committee considered the type of platinum-based chemotherapy should not be restricted to cisplatin.

16.43. The Committee considered that it would be reasonable to treat individuals with an ECOG score of 2 with durvalumab. The Committee noted individuals with a score of ECOG 2 would be eligible for cisplatin treatment, as part of Galsky criteria. The Committee also considered that individuals with an ECOG score of 2 responded well in the trials of other ICI in this setting including in the pembrolizumab in combination with enfortumab vedotin trial (Vulsteke et al. N Engl J Med. 2026).

16.44. The Committee considered it would be appropriate to restrict funding adjuvant treatment to those who had received neoadjuvant durvalumab treatment. The Committee noted that there was currently a lack of data to determine the health benefit of durvalumab treatment in the neoadjuvant setting alone. The Committee considered there was emerging evidence of durvalumab in the neoadjuvant setting.

Summary for assessment

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

Population	People with muscle invasive bladder cancer (MIBC) who are planning to undergo radical cystectomy (RC) and are eligible for platinum-based neoadjuvant chemotherapy (NAC), with a clinical tumour stage of T2, T3, or T4a, N0 or N1, and M0. Patients with prior systemic chemotherapy or immunotherapy for MIBC are excluded, limiting durvalumab treatment to the first line setting.
Intervention	Neoadjuvant durvalumab in combination with NAC, followed by radical cystectomy and adjuvant durvalumab monotherapy: **Neoadjuvant setting:** Durvalumab 1500 mg intravenously every 3 weeks in combination with gemcitabine 2000 mg/m^2 (split-dose) and cisplatin 70 mg/m^2 (GC) for up to 4 cycles. **Adjuvant setting:** Durvalumab 1500 mg intravenously every 4 weeks as monotherapy for up to 8 cycles.
Comparator(s) (NZ context)	Standard of Care represented by NAC, followed by RC, then active surveillance. **Neoadjuvant setting:** Intravenous GC same dosage as intervention **No adjuvant treatment:** Active surveillance
Outcome(s)	Improved Event-free survival (EFS) and Overall Survival (OS) as demonstrated in the NIAGARA Trial (Powles et al NEJM, 2024;391(19):1773-1786): • **EFS-24m** for durvalumab was 67.8% (95% CI, 63.6 to 71.7) compared to 59.8% (95% CI, 55.4 to 64.0) in the comparison group (HR 0.68; 95% CI, 0.56 to 0.82). • **OS-24m** for durvalumab was 82.2% (95% CI, 78.7 to 85.2) compared to 75.2% (95% CI, 71.3 to 78.8) in the comparison group (HR 0.75; 95% CI, 0.59 to 0.93). **Secondary outcomes:** • Non-inferior difference in health-related quality of life (HRQoL) assessed using EORTC QLQ-C30 and EQ-5D-5L • Non-inferior safety profile

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: 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.

17. Emicizumab for haemophilia A, moderate severity, severe bleeding phenotype

Application

17.1. The Committee reviewed the application to widen access to emicizumab for people with moderate severity Haemophilia A with a clinically severe bleeding phenotype.

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

Recommendation

17.3. The Committee **recommended** that access to emicizumab be widened to the treatment of moderate haemophilia A with a clinically severe bleeding with a **high priority**, subject to the following criteria (amendments shown in **bold** and ~~strikethrough~~):

> Initial application – (**Moderate or** severe haemophilia A with or without FVIII inhibitors). Applications only from a haematologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Both:
> 1. Patient has **moderate or** severe congenital haemophilia A ~~with a severe bleeding phenotype~~ (endogenous factor VIII activity less than or equal to ~~2%~~**5%**); and
> 2. **Either:**
>   1. **Individual has a severe bleeding phenotype as determined by the treating haematologist, or**
>   2. **Individual is a child with baseline factor level of 1–3 IU/dL.**
> 2. ~~Emicizumab is to be administered at a dose of no greater than 3 mg/kg weekly for 4 weeks followed by the equivalent of 1.5 mg/kg weekly.~~

17.4. In making their recommendation, the Committee considered that:

17.4.1. Individuals with moderate haemophilia A who have a clinically severe bleeding phenotype have a life-long health need that is comparable to those with severe haemophilia A, the currently funded group.

17.4.2. The available evidence suggests emicizumab will lower the annualised bleed rate in moderate haemophilia A, resulting in better joint health, and lead to an improved quality of life.

17.4.3. The subcutaneous formulation of emicizumab reduced the burden of treatment associated with FVIII concentrate prophylaxis.

17.5. The Committee considered that removing the dose restrictions in the existing access criteria for emicizumab would not lead to greater amount of emicizumab being used per individual.

Discussion

Māori impact

17.6. The Committee discussed the impact of widening access to emicizumab for the treatment of moderate haemophilia A on Māori health areas of focus and Māori health outcomes. Members noted that Māori with haemophilia A (including those with FVIII inhibitors) are overrepresented among those with severe disease and considered it reasonable to assume similar overrepresentation among the population with moderate disease.

Impact on Māori, Pacific peoples, disabled people, and other people who have been underserved by the health system

17.7. The Committee discussed the impact of haemophilia A on Māori, Pacific peoples, disabled people, and other people who have been underserved by the health system.

17.7.1. The Committee was not aware of impacts specific to haemophilia A in this context but acknowledged the disproportionate and detrimental impacts of barriers to access, health literacy, and socioeconomic disadvantage on these groups.

17.7.2. The Committee noted that haemophilia A is not a Māori health areas of focus | Hauora Arotahi.

Background

17.8. The Committee noted that haemophilia A is categorised by an individual's intrinsic factor VIII (FVIII) activity level:

17.8.1. Severe – Intrinsic FVIII is <1% of normal; Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge.

17.8.2. Moderate – Intrinsic FVIII is 1% to 5% of normal; Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery.

17.8.3. Mild – Intrinsic FVIII is 6% to 40% of normal; Severe bleeding with major trauma or surgery; rare spontaneous bleeding.

17.9. The Committee noted that emicizumab is already funded for individuals with severe haemophilia A and the eligibility criteria require an intrinsic FVIII level of 2% of normal or less. The Committee noted that this threshold was set to 2% (and not 1%) to include some individuals with diagnostically moderate disease who exhibit the severe bleeding phenotype.

17.10. The Committee noted the application under review proposed to widen emicizumab access to people with intrinsic FVIII activity levels that are 5% of normal or less.

Health need

17.11. The Committee noted that haemophilia A is a hereditary, life-long bleeding disorder caused by deficiency of coagulation factor VIII, resulting in prolonged spontaneous and injury-related bleeding, progressive joint damage, and potentially life-threatening bleeds.

17.12. The Committee considered there to be a high health need associated with haemophilia A, particularly in children, who are generally more active and where early prophylaxis could prevent long-term damage and disability in adulthood.

17.13. The Committee considered that the health needs of people with moderate haemophilia A who exhibit a clinically severe bleeding phenotype would be comparable to those of people with severe haemophilia A.

17.14. The Committee considered that FVIII levels vary depending on the timing of measurement and are influenced by multiple factors. Members noted that while an individual's intrinsic FVIII activity level is strongly associated with disease severity, their clinical behaviour ultimately defines the bleeding phenotype and should guide treatment selection.

17.15. The Committee noted the current treatment in New Zealand for individuals with moderate haemophilia A who exhibit the severe bleeding phenotype is prophylaxis with FVIII concentrate. Treatment requires frequent infusions (three visits per week) and ongoing monitoring, which members considered highly disruptive to individuals and their whānau,

affecting work and family time and reducing overall quality of life. Treatment can be particularly challenging when individuals are living far from tertiary treatment facilities.

17.16. The Committee discussed the general belief that prophylactic treatment is associated with a reduction in mortality in haemophilia A, although members considered that the available evidence did not readily confirm that an annual bleed rate was a surrogate for survival in this context. The Committee considered that the survival of people with haemophilia is currently comparable to that of the general population in New Zealand, although the disease may be an exacerbating risk factor for the elderly. The Committee considered one of the primary goals of treatment was to prevent disabling muscle and joint deformities and improve people's quality of life.

Health benefit

17.17. The Committee noted the HAVEN 6 study as key evidence, a multicentre, open-label, single-arm, phase III investigation of emicizumab in people with either mild or moderate haemophilia A (FVIII activity 1-40% of normal) without FVIII inhibitors. The study population included 51 participants with moderate haemophilia and 21 with mild disease. Individuals were eligible if their haemophilia A warranted prophylaxis based on the treating physician's assessment. The primary objective of the study was safety.

17.17.1. The Committee noted findings of Négrier et al. Lancet Haematol. 2023;10:e168-77, which reported the primary analysis of the HAVEN 6 study with a median follow-up time of 55.6 weeks.

17.17.1.1. The Committee agreed with the authors 'conclusion that no new safety signals were identified in HAVEN 6. The Committee noted the most common adverse events were headache (17%), injection site reaction (17%), and arthralgia (15%). The Committee did not identify any clinically significant risks associated with emicizumab in the setting of moderate/mild haemophilia A.

17.17.1.2. The Committee noted the efficacy outcomes reported by the primary analysis. The model-based annualised bleeding rate was 2.3 (95% CI: 1.67-3.12) while on treatment with emicizumab, which dropped from an estimated rate of 10.1 pre-emicizumab. Members noted 67% of participants experienced zero treated bleeds. The model-based annualised bleed rate for treated bleeds was 0.9 (95% CI: 0.55-1.52) while on treatment with emicizumab. The Haemophilia Joint Health Score did not worsen over the course of the study compared with baseline. The Committee noted the absence of a control arm, and considered there to be limitations of the baseline metrics given they were retrospective self-reported for the 24 weeks prior to enrolment. Overall, the committee considered the efficacy outcomes should be interpreted as low certainty evidence.

17.17.1.3. The Committee noted that in HAVEN 6, the comprehensive assessment tool of challenges in haemophilia (CATCH) mean scores in the treatment burden domain showed a trend towards improvement with emicizumab but did not reach significance.

17.17.1.4. The Committee considered the evidence to be generalizable and relevant to the New Zealand context and the population requested for funding. The Committee considered that while the HAVEN 6 trial excluded individuals with inhibitors to FVIII, the results would be generalisable to people with inhibitors.

17.17.2. The Committee noted the following observational studies support the findings of HAVEN 6 across different haemophilia severities:

- Buckner et al. Haemophilia. 2026;32:63-70 (severe)
- Lee et al. Ann Acad Med Singap. 2026;52:580-9 (with inhibitors)
- Tory et al. E J Haem. 2024;5:39-46 (moderate)

17.17.3. The Committee noted the findings of Araujo et al. Hematol Transfus Cell Ther. 2025;47:103849, a systematic literature review regarding the efficacy and safety of emicizumab, supports the findings of HAVEN 6.

17.17.4. The Committee noted observational data indicating improvements in the Haemophilia Joint Health Score (HJHS) following initiation of prophylaxis with emicizumab.

- Dutta et al. Ther Adv Hematol. 2026;17
- Dutta et al. Cureus. 2024;16:e74948

17.18. The Committee considered emicizumab to be a highly effective treatment and noted that most people do not experience joint bleeds when adherent to therapy. The Committee noted the significant reduction in treated bleed rates observed in HAVEN 6 and considered the overall body of evidence to be of moderate certainty, noting the limitations of this evidence base (being predominantly from one small, single-arm, open-label study and supporting evidence). The Committee considered that the treatment effect would be meaningful to affected individuals, their caregivers, and their whanau.

17.19. The Committee discussed the association between annualised bleed rate and health-related quality of life reported in the CHESS II trial (Young et al. Orphanet J Rare Dis. 2023;18:227). Members acknowledged differences in the population, treatments, likely costs, and the development of arthropathy. The Committee considered that the EQ-5D-5L is useful; however, it may underestimate disease burden by not capturing factors such as infusion burden, fear of spontaneous bleeding, limitations on recreational activities, and caregiver burden.

17.20. The Committee noted observational data reporting improvements in HRQoL with emicizumab (Mahlangu et al. J Haemophilia. 2019;25:382-91).

Suitability

17.21. The Committee noted that emicizumab is a subcutaneous injection. The dose frequency ranges from once weekly to once monthly.

17.22. The Committee noted the findings of Parnes et al. Haemophilia. 2021;27:e772-5, which reported that most participants from the HAVEN 3 and HAVEN 4 trials preferred emicizumab over their prior treatments (eg. FVIII concentrate) due to the reduced treatment burden of subcutaneous administration.

Cost and savings

17.23. The Committee discussed how widening access to emicizumab would impact the current medical resource utilisation associated with treatment. Members considered that emicizumab would spare infusion related resources, and reduce costs associated with arthropathy and pain. Members considered that emicizumab would be particularly resource-sparing when used in young patients where disabling muscle and joint bleeds can lead to lifelong defects.

17.24. The Committee noted the 2024 World Federation of haemophilia Annual Global Survey, which reported there were 478 people with Haemophilia A in New Zealand. The survey reported that in countries with high-income economies, 45.53% of respondents had severe haemophilia A, 14.64% reported moderate severity, and 39.52% reported mild severity.

17.25. The Committee discussed the uncertainty regarding the proportion of people with moderate haemophilia who would exhibit a clinically severe bleeding phenotype and require prophylaxis. The Committee considered that not all people with moderate haemophilia A would have a severe bleeding phenotype and require prophylaxis with emicizumab.

17.25.1. The Committee noted the findings of Nicola Dario Di Minno et al. Semin Thromb Hemost 2013;39:723-31, a systematic review of arthropathy in people with moderate haemophilia A. The review reported that approximately 30% of people with moderate haemophilia A are prescribed prophylaxis.

17.25.2. The Committee noted a clinical commissioning report released by National Health Service (NHS) in July 2025, titled: Emicizumab for prophylaxis of bleeding episodes in people with moderate haemophilia A without inhibitors (all ages) [URN 2333]. The report states that approximately one quarter to one third of people with moderate haemophilia A required prophylaxis in the UK National Haemophilia Database.

17.25.3. The Committee noted that 51% of participants in the HAVEN 6 trial (which also included mild cases) were receiving FVIII prophylaxis.

17.25.4. The Committee considered that patients with moderate haemophilia A requiring prophylaxis would tend to be more severe cases with 1-3% normal intrinsic Factor VIII. Members considered the remainder of this subset would likely receive on demand/episodic FVIII instead.

17.26. The Committee suggested Pharmac could consider the patient number estimates from the NHS Clinical Commissioning report when estimating the number of likely patients in New Zealand who would become eligible for emicizumab if access were widened. Based on the data included in the NHS report, the Committee considered an additional 20 people (who would likely already be known to treatment services) would become eligible for treatment with emicizumab.

17.27. The Committee considered it would be reasonable to assume an uptake of 80-100% if access to emicizumab were widened.

17.28. The Committee considered that funding emicizumab would largely replace the use of FVIII as prophylactic treatment but noted that some individuals may continue to use FVIII concentrate. The Committee noted that among HAVEN 6 participants who completed a treatment preference survey, 96% reported preferring emicizumab to their prior treatment (Négrier et al. 2023). Members noted a similar finding reported by Parnes et al. Haemophilia. 2021;27:e772-5, where 94% of HAVEN 3 participants who completed the patient preference survey preferred emicizumab to their previous treatment, and 100% of participants in HAVEN 4 expressed a preference for emicizumab.

17.29. The Committee considered the appropriate comparator for emicizumab for people with moderate severity haemophilia A with a clinically severe bleeding phenotype to be prophylaxis with FVIII concentrate. The Committee noted that individuals on emicizumab still require access to FVIII concentrate in the event of major surgery or major trauma. The Committee noted the following dose estimates for episodic FVIII treatments to be reasonable:

17.29.1. Minor bleed (early haemarthrosis, mild muscle bleed, oral bleed): 15-25 IU/kg

17.29.2. Moderate bleed (established joint bleed, deeper muscle bleed): 25-35 IU/kg

17.29.3. Major bleed (severe trauma, GI bleed): 40-50 IU/kg

17.29.4. Life-threatening bleed (intracranial, neck/airway, retroperitoneal): 50 IU/ kg initially; retreating every 8-12 hours

Funding Criteria

17.30. The Committee considered the eligibility criteria included in the NHS Clinical Commissioning report:

> Patients who meet ALL of the following inclusion criteria will be eligible for prophylactic treatment with emicizumab:
>
> - A confirmed diagnosis of moderate haemophilia A (defined as FVIII levels ≥ 1% and ≤ 5%
> AND
> - A severe phenotype, fulfilling ONE of the following criteria:
> - Joint damage or any joint bleeds in a year
> OR
> - More than 3 treated bleeds in 12 months
> OR
> - Currently receiving prophylaxis with FVIII for more than 12 weeks
> OR
> - Children with baseline factor levels of 1-3IU/dL

17.31. The Committee considered that a FVIII threshold of ≤3% would capture most people with moderate haemophilia A who have a severe bleeding phenotype and was aware of 16 individuals in the Auckland/ Northland region who would be in this category.

17.32. Members suggested Pharmac could consider delineating access for those with FVIII levels of 4–5% and considered that a greater proportion of individuals in this group are likely to have a milder bleeding phenotype. The Committee noted that individuals with FVIII levels of 4–5% who have a severe bleeding phenotype would most likely already be receiving FVIII prophylaxis and should be eligible to switch to emicizumab if access were widened. Members considered that tor the individuals with FVIII levels of 4–5% who are not on prophylaxis (likely young patients whose bleeding phenotype has not been revealed), those who have had a significant spontaneous bleed (eg. joint bleed) would be considered for prophylaxis and should be eligible for emicizumab.

17.32.1. Overall, the Committee considered the criteria developed by the NHS would be a logical extension to the current access criteria and present a pragmatic way for the moderate patients with severe bleeding phenotype to have timely access to treatment, while excluding those who are unlikely to require emicizumab (eg mild bleeding phenotype).

17.33. The Committee discussed the challenges in defining a clinically severe bleeding phenotype and considered that, in practice, it would be pragmatic to leave this to the discretion of the treating haematologist.

17.34. The Committee acknowledged the importance of implementing criteria that do not require people to have experienced multiple bleeds or have developed a target joint prior to accessing treatment. Members noted the value of having early access to prophylaxis to prevent disabling muscles and joint damage.

17.35. The Committee discussed the potential inclusion of people with mild haemophilia A and considered that individuals with mild disease who experience frequent bleeds are highly uncommon and are likely to have additional factors contributing to their clinically severe bleeding phenotype. Members considered these individuals would be more appropriately considered through Pharmac's Exceptional Circumstances Framework.

17.36. The Committee considered emicizumab would not be necessary for an individual moderate haemophilia A with a mild bleeding phenotype, who would be more appropriately managed with episodic treatment with FVIII concentrate as required.

17.37. The Committee considered that removing the dose restrictions in the existing access criteria for emicizumab would not lead to greater amount of emicizumab being used per individual.

Summary for assessment

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

Population	Adults with moderate haemophilia A (3% to 5% of normal intrinsic Factor VIII, inclusive) with a clinically severe bleeding phenotype AND children with FVIII 1-3 IU/dL.
Intervention	Emicizumab (SC) - Loading dose of 3mg/kg SC weekly for 4 weeks followed by either 1.5mg/kg SC weekly, 3mg/kg SC weekly or 6mg/kg SC four weekly, indefinitely.
Comparator(s)	Extended or Short half-life prophylactic Factor VIII Concentrate – IV infusion given 2-3 times weekly (likely the majority of people), or On-demand/episodic Factor III Concentrate
Outcome(s)	**Reduction in annual bleeds** • All-bleed annualised bleed rates were 10.1 (95% CI 6.93–14.76) from 24 weeks pre-study and 2.3 (1.67–3·12) on-study after a median follow-up of 55.6 weeks. (HAVEN 6 trial - Négrier et al. 2023) **Reduced in annual bleeds requiring treatment** • 67% of participants experienced zero treated bleeds. • Annualised bleed rate for treated bleeds was 0.9 (95% CI: 0.55-1.52) while on treatment with emicizumab. (HAVEN 6 trial - Négrier et al. 2023) **Improved health-related quality of life (magnitude of benefit uncertain)** • Relationship between annual bleed rate and HRQoL (Young et al. Orphanet J Rare Dis. 2023;18:227). • Demonstrated improvement in utility with emicizumab in HAVEN 3 and 4 trials (Mahlangu et al. N Engl J Med. 2018;379:811-22, Pipe et al. Lancet Haematol. 2019;6:e295-e305)
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.	

18. Aflibercept (Eylea) 8mg pre-filled syringe for visual impairment caused by subfoveal choroidal neovascularisation (CNV) secondary to age-related macular degeneration and diabetic macular oedema

Application

18.1. The Committee reviewed the application for aflibercept 8 mg pre-filled syringe (PFS) in the treatment of visual impairment caused by subfoveal choroidal neovascularisation secondary to (wet) age-related macular degeneration (wAMD) and diabetic macular oedema (DMO).

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

Recommendation

18.3. The Committee **recommended** that aflibercept 8 mg pre-filled syringe (PFS) for the treatment of visual impairment caused by subfoveal choroidal neovascularisation secondary to (wet) age-related macular degeneration (wAMD) and diabetic oedema (DMO) be funded **only if cost neutral to aflibercept 2 mg and faricimab 6 mg,** subject to the same Special Authority criteria, as follows:

Initial application — (diabetic macular oedema) from any relevant practitioner. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 Patient has centre involving diabetic macular oedema (DMO); and
2 Patient's disease is non responsive to 4 doses of intravitreal bevacizumab when administered 4-6 weekly; and
3 Patient has reduced visual acuity between 6/9 – 6/36 with functional awareness of reduction in vision; and
4 Patient has DMO within central OCT (ocular coherence tomography) subfield > 350 micrometers; and
5 There is no centre-involving sub-retinal fibrosis or foveal atrophy; and
6 Patient has not previously been treated with faricimab for longer than 3 months

Renewal — (diabetic macular oedema) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:
1 There is stability or two lines of Snellen visual acuity gain; and
2 There is structural improvement on OCT scan (with reduction in intra-retinal cysts, central retinal thickness, and sub-retinal fluid); and
3 Patient's vision is 6/36 or better on the Snellen visual acuity score; and
4 There is no centre-involving sub-retinal fibrosis or foveal atrophy.

Initial application — (wet age-related macular degeneration) from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
Either:
1 All of the following:
1.1 Any of the following:
1.1.1 Wet age-related macular degeneration (wet AMD); or
1.1.2 Polypoidal choroidal vasculopathy; or
1.1.3 Choroidal neovascular membrane from causes other than wet AMD; and
1.2 Either:
1.2.1 The patient has developed severe endophthalmitis or severe posterior uveitis following treatment with bevacizumab; or
1.2.2 There is worsening of vision or failure of retina to dry despite three intraocular injections of bevacizumab four weeks apart; and
1.3 There is no structural damage to the central fovea of the treated eye; and
1.4 Patient has not previously been treated with ranibizumab or faricimab for longer than 3 months; or
2 Either:
2.1 Patient has current approval to use ranibizumab or faricimab for treatment of wAMD and was found to be intolerant within 3 months; or

2.2 Patient has previously* (*before June 2018) received treatment with ranibizumab for wAMD and disease was stable while on treatment.

Renewal — (wet age-related macular degeneration) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1 Documented benefit must be demonstrated to continue; and
2 Patient's vision is 6/36 or better on the Snellen visual acuity score; and
3 There is no structural damage to the central fovea of the treated eye.

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

18.4.1. For the treatment of wAMD and DMO, the health benefit and safety profile is non-inferior between aflibercept 8 mg PFS and aflibercept 2 mg and faricimab.

18.4.2. Intervals between injections would be extended using aflibercept 8 mg compared to aflibercept 2 mg, which would reduce injection burden for patients as well as alleviating pressures on ophthalmological services.

Discussion

Māori impact

18.5. The Committee discussed the impact of funding aflibercept 8 mg PFS for the treatment of wAMD and DMO on Māori health areas of focus and Māori health outcomes. The Committee noted that diabetes disproportionately impacts Māori and diabetes and is one of Pharmac's Hauora Arotahi - Māori health area of focus: Matehuka - Diabetes.

18.6. The Committee considered that higher rates of DMO would be expected in Māori, however, data is lacking. The Committee noted evidence in the application that reported Māori were approximately twice as likely to never receive diabetes eye care or to access ophthalmology clinics when referred, compared to New Zealand Europeans (Silwal et al. PLoS One. 2023; PTAC record Feb 2024). From the same study, the Committee also noted Māori were 10% less likely to receive biennial screening and received the fewest anti-vascular endothelial growth factor (VEGF) injections when treatment was commenced compared to Europeans (Silwal et al. 2023, PTAC record Feb 2024).

18.7. The Committee considered that there is limited information reporting health outcomes of wAMD among Māori. The Committee considered that the lower uptake of anti-VEGF treatment by Māori reported in Silwal et al. 2023 would impact wAMD treatment.

Populations with high health needs

18.8. The Committee discussed the health need(s) of Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee noted disproportionate prevalence of diabetes in Pacific peoples, as evidenced in ethnicity data reporting that Pacific peoples have the highest rates of diabetes per population in New Zealand (Te Whatu Ora – Health, NZ Virtual Diabetes Register. 2025).

18.9. The Committee discussed the impact of funding aflibercept 8 mg and noted that Pacific peoples show significantly lower rates of anti-VEGF treatment and reduced access to ophthalmological services compared to Europeans (Silwal et al. 2023).

Background

18.10. The Committee noted currently funded treatments for wAMD and DMO:

18.10.1. Bevacizumab (Listed Hospital and Community) – funded for ocular neovascularisation and exudative ocular angiopathy, typically first-line use.

18.10.2. Ranibizumab (listed Hospital only) – funded for wAMD, typically funded second-line use.

18.10.3. Aflibercept 2 mg (Listed Community and Hospital Schedule) – funded for wAMD and DMO, typically funded second-line use.

18.10.4. Faricimab 6 mg vial (Listed Community and Hospital Schedule) – funded for wAMD and DMO, typically funded second-line use; similar to aflibercept 2 mg.

Health need

18.11. The Committee noted the health needs of people with wAMD and DMO were previously discussed at the Feb 2024 PTAC meeting when considering an application for faricimab (PTAC record Feb 2024).

18.12. The Committee noted that age-related macular degeneration (AMD) is a progressive degenerative disease of the central retina (macula), an area of the retina responsible for visual acuity and colour vision. Neovascular (wet) AMD (wAMD) is an advanced stage of AMD and is characterised by the abnormal formation of new blood vessels beneath the macula. These vessels may leak fluid and/or blood into the inner retinal layers/subretinal space. This disrupts the overlying structures, including the Bruch's membrane, the retinal pigment epithelia and the photoreceptors resulting in focal retinal detachment and vision loss (van Lookeren Campagne et al. J Pathol. 2014; PTAC record Feb 2024).

18.13. The Committee noted that in diabetes, elevated blood glucose levels may lead to damage to the small blood vessels within the retina, resulting in diabetic retinopathy. DMO is an advanced and serious manifestation of diabetic retinopathy. DMO is characterised by an accumulation of fluid at the macula, which is the highly sensitive area of the retina responsible for sharp central vision (Tan et al. Lancet Diabetes Endocrinol. 2017). The condition is associated with a loss of central vision, measured as a reduction in best-corrected visual acuity (BCVA); and is a major cause of vision loss (PTAC record Feb 2024).

18.14. The Committee noted that both wAMD and DMO lead to irreversible vision loss, a reduction in an individual's ability to perform daily tasks and is associated with depression.

18.15. The Committee noted that the current funded first-line treatment for both wAMD and DMO is bevacizumab. The Committee noted funded second-line treatment options for wAMD are faricimab, aflibercept 2 mg, and ranibizumab, although ranibizumab is listed on the Hospital Schedule only. The Committee noted the funded second-line treatment options for DMO are faricimab and aflibercept 2 mg. The Committee noted the dosing frequency for aflibercept 8 mg in the application is reduced compared to current second-line treatments.

18.16. The Committee noted that ocular injections associated with wAMD and DMO treatment are a source of discomfort and distress for patients. Patients have indicated that a reduction in the frequency of injections and appointments would provide health benefit (PTAC record Feb 2024; Sivaprasad et al. Clin Ophthamol. 2016).

Health benefit

18.17. The Committee noted that aflibercept is a vascular endothelial growth factor (VEGF) inhibitor and is currently funded in the form of 2 mg vials.

18.18. The Committee noted the proposed aflibercept 8 mg treatment paradigm for wAMD and DMO as provided by the applicant.

18.18.1. The Committee noted that aflibercept 8 mg, aflibercept 2 mg, and faricimab all use extended-interval maintenance dosing following initial loading phases. The Committee noted that the application estimates aflibercept 8 mg will have the longest dosing intervals. The Committee noted for both wAMD and DMO, aflibercept 8 mg is estimated to allow maintenance dosing every 8–16 weeks, with the potential to extend dosing intervals to up to 20 weeks after 52 weeks of treatment.

18.18.2. The Committee noted by comparison, faricimab dosing intervals are determined according to disease activity and may be extended to 16 weeks in patients without disease activity, while aflibercept 2 mg is generally administered every 8 weeks during maintenance treatment, with interval extension possible in some patients using a treat-and-extend approach.

18.19. The Committee noted the PULSAR trial, a phase 3, randomised, double-masked, active-controlled, non-inferiority trial as key evidence of aflibercept for the treatment for wAMD (Lanzetta et al. Lancet. 2024). The Committee noted the duration of the main phase was 96 weeks.

18.19.1. The Committee noted that patients were randomised to one of three treatment groups: intravitreal aflibercept 2 mg every eight weeks (2 mg q8w; n=336), aflibercept 8 mg every 12 weeks (8 mg q12w; n=335), or aflibercept 8 mg every 16 weeks (8 mg q16w; n=338), following three initial monthly doses. The Committee noted that 76% of patients were Caucasian and 4% of patients had previously received VEGF inhibitor treatment for AMD.

18.19.2. The Committee noted the primary outcome was BCVA after 48 weeks, with a non-inferiority margin of four letters. The Committee noted that aflibercept 8 mg q12w and 8 mg q16w showed non-inferiority compared with aflibercept 2 mg q8w. Compared to aflibercept 2 mg q8w, mean differences in BCVA change from baseline were -0.97 letters (95% CI -2.87 to 0.92) and -1.14 letters (95% CI -2.97 to 0.69) for aflibercept 8 mg q12w and 8 mg q16w, respectively.

18.20. The Committee noted the PHOTON trial, a phase 2/3, randomised, double-masked, active-controlled, non-inferiority trial as key evidence of aflibercept for the treatment of DMO (Brown et al. Lancet. 2024). The Committee noted the duration of the main phase was 96 weeks.

18.20.1. The Committee noted that patients were randomised to one of three treatment groups: intravitreal aflibercept 2 mg every 8 weeks (2 mg q8w; n=167) vs aflibercept 8 mg every 12 weeks (8 mg q12w; n=329) vs aflibercept 8 mg every 16 weeks (8 mg q16w; n=164). The Committee noted that 72% of patients were Caucasian and 44% of patients had previously received VEGF inhibitor treatment for DMO.

18.20.2. The Committee noted that treatment intervals were shortened to 8 weeks in cases where a greater than 10 letter loss was observed or a 50 µm increase in central retinal thickness (CRT) was observed.

18.20.3. The Committee noted the primary outcome was BCVA after 48 weeks with a non-inferiority margin of 4 letters. The Committee noted that the aflibercept 8 mg q12w and 8 mg q16w groups showed non-inferior BCVA gains compared with aflibercept 2 mg q8w. The difference in least square means was -0.57 letters (95% CI -2.26 to 1.13, *p* value for non-inferiority <0.0001) between 8 mg q12w and 2 mg q8w and -1.44 letters (95% CI -3.27 to 0.39, *p* value for non-inferiority = 0.0031) between 8 mg q16w and 2 mg q8w.

18.20.4. The Committee noted mean reductions in CRT compared to baseline were observed across all treatment groups at 48 weeks. The least squares mean

change was -176.8 µm (95% CI -188.0 to -165.5) in the aflibercept 8 mg q12w group, -148.8 µm (-167.5 to -130.2) in the 8 mg q16w group, and -164.8 µm (-182.2 to -147.5) in the 2 mg q8w group.

18.20.5. The Committee noted subgroup analyses conducted by the applicant derived from PHOTON trial data, specifically data reporting efficacy of 8 mg q12/16w vs 2 mg q8w if patients had or had not received prior anti-VEGF treatment. The Committee noted no significant differences in BCVA at 48 weeks between aflibercept 8 mg (both groups) and aflibercept 2 mg irrespective of prior treatment status.

18.21. The Committee considered the evidence of non-inferiority from both the PULSAR and PHOTON trials to be high quality. The Committee considered indirect comparisons across trials inferred overall similarity of three treatments with respect to efficacy (aflibercept 2 mg, aflibercept 8mg, and faricimab).

18.22. The Committee noted the safety data provided by the applicant, which was pooled data from both PULSAR and PHOTON trials, as well as the smaller CANDELA trial (Wykoff et al. JAMA Ophthalmology. 2023). The Committee considered the safety profile of the aflibercept 8 mg groups to be similar to that of aflibercept 2 mg q8w.

18.22.1. The Committee considered that the reported percentage of patients with cataracts following aflibercept treatment was numerically higher in the 8 mg groups (combined average 8.2%) vs 2 mg q8w (5.0%), however, as the *p* value was not reported the Committee considered this was likely an insignificant difference.

18.22.2. The Committee noted additional research into the rates of cataracts in treated vs untreated eyes and reported that up to 40% of treated patients may require cataract surgery in years following treatment.

18.23. The Committee noted the non-inferiority trials comparing faricimab versus aflibercept 2 mg q8w for treatment of DMO and summarised primary outcome (BCVA) data (YOSEMITE and RHINE trials: Eter et al. Ophthalmol Sci. 2021). The Committee noted 75% of patients were treatment naïve, which differs from the target population in the application who would receive aflibercept in the second line. The Committee noted there was no difference in mean BCVA scores at one year (averaged over weeks 48, 52, and 56) between faricimab and aflibercept.

18.24. The Committee noted primary outcome (BCVA) data from non-inferiority trials comparing faricimab with aflibercept 2 mg q8w in wAMD (TENAYA and LUCERNE trials: Khanani et al. Ophthalmology. 2024). The Committee noted all patients were treatment naïve. The Committee noted non-inferiority in mean change from baseline BCVA (averaged over weeks 40, 44, and 48) across both groups.

18.25. The Committee noted evidence reviewing anti-VEGF therapies for DMO, which concluded that limited evidence exists for the comparative efficacy and safety of anti-VEGF for DMO beyond the one-year follow-up (Virgili et al. Cochrane Database Syst Rev. 2023).

18.26. The Committee noted a systematic review of intravitreal anti-VEGF therapies, which reported treatment with faricimab 6 mg or aflibercept 8 mg appeared to provide the "optimal balance between treatment outcomes, anatomical outcomes, and lowest treatment burden" (Butler et al. Acta Ophthalmol. 2025).

18.27. The Committee considered there is a potential subgroup of patients who are non-responsive to aflibercept 2 mg who may respond to aflibercept 8 mg. The Committee considered that this may occur if the patient is non-responsive to treatment after less than three months. The Committee considered some patients may benefit from taking the

higher dose at the same interval as aflibercept 2 mg, although clinical trial evidence is lacking.

Suitability

18.28. The Committee considered that aflibercept 8mg comes as a pre-filled syringe versus the vial provided for 2 mg, which may enable easier use in the clinic.

18.29. The Committee considered the injection frequency for the proposed patient population based on those provided by the PULSAR and PHOTON trials. The Committee noted that these trials may overestimate treatment extension in the New Zealand population as the majority of trial participants were treatment naïve, whereas patients in New Zealand would receive aflibercept or faricimab second line. The Committee considered that treatment-experienced New Zealand patients may require more frequent maintenance dosing compared to treatment naïve patients.

18.29.1. The Committee noted supplier data based on findings from the PHOTON trial, which reported that aflibercept 8 mg required fewer injections than aflibercept 2 mg through both week 60 and week 96. The data reported through Week 156, over 80% of patients originally treated with aflibercept 8 mg maintained dosing intervals of at least 12 weeks without needing interval shortening, and nearly 70%, 48%, and 28% achieved final treatment intervals of at least 16, 20, and 24 weeks, respectively.

18.29.2. The Committee noted the PULSAR findings that reported 78% of patients on aflibercept 8 mg were able to extend to ≥ 16-week dosing intervals, averaging to around three injections a year. The Committee considered this was optimistic and would likely be closer to four per year in the New Zealand clinical context.

18.29.3. The Committee noted email advice from members of the Ophthalmology Special Advisory Committee (SAC). The advice indicated that:

18.29.3.1. Those receiving aflibercept 8 mg as second-line treatment would unlikely have intervals that extend past three months.

18.29.3.2. Those receiving aflibercept 8 mg or faricimab would likely receive 4-6 injections annually.

18.29.3.3. Patients receiving aflibercept 2 mg likely receive 6-8 injections per year.

18.30. The Committee noted evidence from switching studies where patients with wAMD and DMO receiving anti-VEGF therapy switched to faricimab and reported longer treatment intervals of 6-11 weeks (five to nine injections per year) (Wong et al. BMJ Open Ophthalmol. 2025).

18.31. The Committee considered that the frequency of aflibercept 8 mg injections would be similar to faricimab and 4-6 injections annually was a reasonable estimate.

18.32. The Committee noted, overall, that aflibercept 8 mg would result in reduced injection frequency compared to currently funded aflibercept 2 mg.

18.32.1. The Committee noted this would benefit the patient as well as Ophthalmology services where capacity issues are significant.

18.32.2. The Committee noted that reduced injection frequency was unlikely to lower the risk of endophthalmitis.

Cost and savings

18.33. The Committee considered that costs per patient for aflibercept 8 mg should likely reflect a higher number of annual injections at maintenance compared to the trial evidence, given that most trial participants were treatment naïve.

18.34. The Committee considered that, if funded, most patients currently receiving aflibercept 2 mg would be expected to switch to aflibercept 8 mg.

18.35. The Committee considered advice from the Ophthalmology SAC estimating an approximate 50/50 split between aflibercept 8 mg and faricimab as second-line treatments and considered that this seemed reasonable. The Committee considered that faricimab may remain a preferred option among some clinicians given that faricimab may achieve a slightly greater reduction in subfoveal thickness (with similar overall visual acuity improvements to aflibercept 8 mg).

Funding criteria

18.36. The Committee considered that the existing funding criteria for aflibercept 2 mg was appropriate for aflibercept 8 mg.

Summary for assessment

18.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for aflibercept 8 mg PFS if it were to be funded in New Zealand for wAMD and DMO. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

	wAMD	DMO

Population	People with wAMD who do not experience therapeutic response to bevacizumab, or who have developed severe endophthalmitis, or severe posterior uveitis following treatment with bevacizumab. People who are receiving aflibercept 2 mg. People who are receiving faricimab or ranibizumab for wAMD but experience intolerance to treatment within 3 months of commencing treatment.	People with DMO who do not experience therapeutic response to bevacizumab. People who are receiving aflibercept 2 mg. People not previously treated with faricimab for longer than 3 months.
Intervention	Aflibercept 8mg prefilled syringe (PFS) administered at 4 weekly intervals for the first three (3) months, with dosing intervals then extended up to every 16 weeks. In wAMD, treatment is for life.	Aflibercept 8mg PFS administered at 4 weekly intervals for the first three (3) months, with dosing intervals then extended up to every 16 weeks. In DMO treatment may be paused for some time until vision begins to deteriorate again
Comparator(s) (NZ context)	<u>Aflibercept 2mg injection</u> Once per eye every 4 weeks for 3 consecutive months. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks. <u>Faricimab 6 mg injection</u> Every 4 weeks for the first 4 doses. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks (4 months), in increments of 4 weeks.	<u>Aflibercept 2 mg injection</u> Every 4 weeks (monthly) for five months, followed by one injection every 8 weeks (two months). After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. <u>Faricimab 6 mg injection</u> every 4 weeks for the first 4 doses. Thereafter, a treat-and-extend approach is used. The dosing interval may be extended up to every 16 weeks, in increments of 4 weeks.
Outcome(s)	Non-inferiority to other anti-VEGF treatments in maintaining or improving clearness or sharpness of vision. Extended treatment interval compared to aflibercept 2 mg.	

<u>Table definitions:</u>

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target 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.