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 15 February & 16 February 2024

1. Present

PTAC members:
Jane Thomas (Chair)
Rhiannon Braund (Deputy Chair)
Brian Anderson
Bruce King
Elizabeth Dennett
Helen Evans
James Le Fevre
John Mottershead
Liza Lack
Matthew Dawes
Matthew Strother
Paul Vroegop
Robyn Manuel
Stephen Munn

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. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
8.5	Funding criteria for vedolizumab for currently funded inflammatory bowel disease indications be amended to allow dose frequency escalation in individuals with primary non-response to vedolizumab	Low priority

8.7	Funding criteria for vedolizumab for currently funded inflammatory bowel disease indications be amended to allow for dose frequency escalation in individuals with secondary loss of response to vedolizumab	High priority
9.3	Esketamine for treatment-resistant depression post augmentation	Decline
10.3	Phosphodiesterase 5 inhibitors (PDE5i) for treatment of erectile dysfunction following prostate cancer treatment, subject to Special Authority criteria	High priority
11.3	Naloxone nasal spray for use by emergency medical service personnel	Low priority
11.5	Naloxone nasal spray for use by non-paramedic first responders (ie fire service, police)	High priority
11.7	Naloxone nasal spray for individuals at high risk of opioid overdose	High priority
12.3	Faricimab for the second line treatment of diabetic macular oedema subject to Special Authority criteria	Cost neutral
13.3	Faricimab for the second line treatment of (wet) age related macular degeneration subject to Special Authority criteria	Cost neutral

4. Record of PTAC meeting held 16 November & 17 November

4.1. The Committee reviewed the records of the PTAC meeting held on 16 November & 17 November 2023.

4.2. The Committee accepted the record.

5. Action Points

5.1. There are no current action points.

6. Pharmac Update

6.1. The Committee noted the Pharmac Update.

7. Specialist Advisory Committee Records

21 July 2023 Cancer Treatments Advisory Committee meeting record

7.1. The Committee (PTAC) reviewed the records of the Cancer Treatments Advisory Committee held on 21 July 2023.

7.2. PTAC noted the records, including the Advisory Committee's recommendations.

19 September 2023 Neurological Advisory Committee meeting record

7.3. The Committee (PTAC) reviewed the record of the Neurological Advisory Committee meeting held on 19 November 2023.

7.4. PTAC noted the record, including the Advisory Committee's recommendations.

7.5. PTAC noted the Advisory Committee's recommendation that rotigotine be listed with a high priority. PTAC agreed with the Advisory Committee's recommendation based on its expert advice about the treatment paradigm for Parkinson's disease.

8. Matters arising: Vedolizumab - Ulcerative colitis and Crohn's disease, removal of the current dose frequency restriction

Application

8.1. The Committee noted that Pharmac staff sought the Committee's view of the potential health benefits associated with vedolizumab maintenance dose frequency escalation to 300 mg every four weeks (Q4W) for people whose disease has either not responded, or has lost response, to vedolizumab for the treatment of Crohn's disease (CD) or ulcerative colitis (UC).

8.2. The Committee noted that Pharmac received a letter dated 25 November 2022 from Takeda, the supplier of vedolizumab. The letter requested the Special Authority restriction for vedolizumab include an option for dose escalation in maintenance dosing frequency to 300 mg Q4W for those who experience a loss of clinical response, and the option for a fourth induction dose at week 10 for people with CD who have not had a response.

8.3. The Committee noted that, in response to the late 2022 consultation regarding the proposal to fund vedolizumab for CD and UC, Pharmac received a response requesting that dose escalation of vedolizumab be considered. The response was submitted on behalf of the NZIBDNG (New Zealand Inflammatory Bowel Disease Nurses Group).

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

Recommendation

8.5. The Committee **recommended** that the funding criteria for vedolizumab for currently funded inflammatory bowel disease indications be amended to allow a fourth induction dose at week 10, and subsequently a maintenance dose frequency escalation (up to four-weekly dosing as clinically indicated), in individuals with primary non-response (PNR) to vedolizumab at week six, with a **low priority**.

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

- Dose escalation for those experiencing PNR to vedolizumab would offer people with IBD an additional chance to benefit (about 30%) from this medicine in later lines of treatment where there are few options remaining to switch to.
- The evidence in this context was of low quality, however, induction dose escalation aligns with the Medsafe data sheet and may be clinically appropriate.

8.7. The Committee **recommended** that the funding criteria for vedolizumab for currently funded inflammatory bowel disease indications be amended to allow for a maintenance dose frequency escalation (up to four-weekly dosing as clinically indicated) in individuals with secondary loss of response (SLOR) to vedolizumab, with a **high priority**.

8.8. In making this recommendation, the Committee considered that there was high quality evidence for vedolizumab dose escalation for SLOR and noted that this aligns with international practice.

Discussion

Māori impact

8.9. The Committee discussed the impact of funding a dose frequency escalation of vedolizumab for the treatment of inflammatory bowel disease (IBD) indications on Māori health areas of focus and Māori health outcomes. Members considered that Māori experience lower rates of IBD compared with non-Māori, however, that rates of IBD for Māori were increasing.

8.10. Members considered that IBD is challenging to control and that, compared with non-Māori, Māori with IBD and complex comorbidities (such as diabetes) experience a greater impact from IBD due to the difficulty of managing this disease alongside other comorbidities.

8.11. Members noted that the evidence for vedolizumab dose escalation for IBD indications did not include Māori participants.

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

8.12. The Committee did not have specific comments regarding the impact of funding a dose frequency escalation of vedolizumab for the treatment of IBD indications on groups who have been underserved by the health system.

Background

8.13. The Committee noted that vedolizumab has been funded since 1 February 2023 for moderate to severe active Crohn's disease (CD) or ulcerative colitis (UC) that has not responded to prior treatments, subject to restriction criteria. The Committee noted that the funding criteria currently include the following dose frequency-limiting criterion within the renewal application, relating to the maintenance period: "Vedolizumab will be used at a dose no greater than 300 mg intravenously every eight weeks".

8.14. The Committee noted that vedolizumab was considered by the Gastrointestinal Subcommittee in March 2017, and in November 2020 by PTAC. The Committee noted that neither Committee made specific recommendations regarding dose escalation at those meetings.

8.15. The Committee noted the current status of funding of dose escalation for other biologic treatments for IBD:

8.15.1. The criteria for adalimumab permit the funded use of escalated doses as there is no dose restriction; this was removed from all funded indications in March 2022 with the widening of access resulting from the adalimumab Request for Proposals.

8.15.2. Pharmac has ranked an application for infliximab for CD and UC - widening access (dose escalation) as an option for investment.

8.15.3. The criteria for ustekinumab include a dose-limiting criterion within the renewal, consistent with the recommendations from PTAC (May 2018 and February 2019) and the Gastrointestinal Subcommittee (October 2018) to fund ustekinumab for IBD indications with a dose restriction of 90 mg per eight weeks. Evidence to support further dose escalation of ustekinumab in this population group would need to be reviewed in full, via a funding application for consideration of dose escalation.

8.16. The Committee considered that where vedolizumab is used early in the treatment of IBD (ie first-line use) but does not provide sufficient response, individuals are likely to receive another biologic treatment. However, the Committee considered that there is variation in clinical practice and preferences for pharmaceutical or surgical management of IBD, which can also differ between CD and UC. The Committee considered that some clinicians prefer earlier surgery after few biologic treatments as gut tissue is less affected, while others prefer to avoid colectomy if possible, and in some cases additional time is needed for individuals with IBD to decide their preferred course of treatment.

Primary non-response (PNR)

8.17. The Committee noted that PNR occurs in around 40% of people with UC or CD who receive vedolizumab. The Committee noted that strategies to control disease where PNR has occurred involve either changing to another biologic treatment or increasing the frequency of doses by decreasing the dosing interval. The Committee noted that vedolizumab's Medsafe data sheet includes a recommendation to discontinue treatment if there is no response at 14 weeks, with this timing being appropriate to indicate instances when disease is primarily unresponsive despite dose optimisation.

8.18. The Committee considered that Pharmac could expect to receive Named Patient Pharmaceutical Applications (NPPAs) for four-weekly (Q4W) dosing of individuals where PNR has been experienced with last-line use of vedolizumab.

8.19. The Committee was made aware of the following evidence for vedolizumab dose escalation in cases of PNR:

8.19.1. A 'real-world' observational cohort of 788 individuals with CD or UC (Schmidt et al. Inflamm Bowel Dis. 2018;24:2461-7). Of 51 participants who underwent dose escalation for non-response to vedolizumab, including 15 patients with PNR, 29% experienced a treatment response.

8.19.1.1. Members considered that the proportion of people experiencing PNR who received dose escalation in this study was lower than what would be expected in New Zealand, as most other jurisdictions have another medicine to switch to if there is no response at week six or 10. The Committee therefore considered that the proportion of people with PNR likely to receive dose escalation, if funded in New Zealand, would be higher.

8.19.2. A case series of 47 individuals with IBD who were treated with vedolizumab, for whom PNR occurred in 43% (Willet et al. Clin Gastro Hepatol. 2017;15:1750-7). All participants with PNR at week 10 underwent dose escalation and of these, 75% experienced a treatment response. Members noted these proportions were very different to those reported by Schmidt et al.

8.19.3. A retrospective database study reported treatment response to vedolizumab dose escalation in two of 13 (15%) of people with IBD who experienced PNR and 15/23 (65%) of people who experienced secondary loss of response (SLOR) following positive primary response (Zelinkova et al. J Crohns Colitis. 2021;15 (Suppl 1):S454).

8.19.4. A retrospective cohort study reported response to vedolizumab dose escalation in zero of six people with CD with PNR to vedolizumab (Zanoni Dotti et al. Crohns Colitis 360. 2023;5:1-8).

8.20. The Committee considered that there was low quality evidence for vedolizumab dose frequency escalation in PNR and that this applied to both CD and UC. The Committee

considered that it was not possible to determine if response rates differed between studies due to the small numbers of individuals with PNR.

Secondary loss of response (SLOR)

8.21. Members considered that people for whom anti-TNF treatments fail despite dose escalation would be more likely to experience poor responses to subsequent treatments and have a greater chance of experiencing SLOR on standard vedolizumab dosing.

8.22. Members considered that the mechanism by which SLOR to vedolizumab occurs relates to the drug target more than drug concentration, thus the treatment itself is not likely to give good effect in all cases and any effect would be expected to wane over time.

8.23. The Committee noted the following evidence for vedolizumab dose escalation in cases of SLOR:

8.23.1. A meta-analysis reporting that 48% of those with CD and 40% with UC experienced SLOR, and 54% of those with SLOR subsequently received a response to dose escalation (Peyrin-Biroulet et al. (Clin Gastroenterol Hepatol. 2019;17:838-46.e2).

8.23.2. A meta-analysis reporting that loss of response is common and that about half of people with SLOR will experience a treatment response to increasing the vedolizumab dose (Patel et al. (Crohns Colitis 360. 2022;4:otac020).

8.23.3. A publication providing longer term data in UC including overall survival and clinical remission rates (a more stringent measure). The authors reported that about a third of people experience a response but the response wanes with time (Loftus et al. Aliment Pharmacol Ther. 2020;52:1353-65).

8.24. The Committee was also made aware or reminded of the following evidence for vedolizumab dose escalation in cases of SLOR:

8.24.1. Outtier et al. GastroHep. 2021;3:63-71. This prospective study in 59 people with IBD with secondary loss of response to Q8W maintenance therapy reported an increase in median trough concentration with Q4W dosing and recapture of clinical response occurring in 54% of participants at week eight.

8.24.2. Vermeire et al. J. Crohns Colitis. 2017;11:412-24. This study included individuals with CD from GEMINI studies and reported clinical responses in 54% of participants at 28 weeks post dose escalation and in 35% at 100 weeks.

8.24.3. Zelinkova et al. J Crohns Colitis. 2021;15 (Suppl 1):S454. Treatment response to vedolizumab recaptured after dose frequency escalation in 15/23 (65%) of people with IBD with SLOR, alongside two of 13 responses (15%) for people with PNR.

8.24.4. Panaccione et al. Adv Ther. 2023;40:2051-81. Dose escalation of vedolizumab occurred in approximately a third of those with IBD internationally. Members considered that this would occur more commonly in populations receiving vedolizumab for IBD outside the US due to availability of fewer treatment options than in the US.

8.25. The Committee considered that there was high quality evidence for the efficacy and safety of vedolizumab dose escalation in SLOR.

Evidence in PNR and SLOR

8.26. The Committee was made aware of evidence that clinical response to dose escalation for either PNR or SLOR wanes with time (Hilley et al. J Crohn's Colitis. 2022;Suppl_1:P594). The Committee noted this Australian study reported 24% of people persisted on vedolizumab 12 months post-escalation and its authors had considered this rate low.

8.27. The Committee was made aware of evidence reporting that those people with UC on higher doses of vedolizumab were more likely to be symptomatic, less likely to be in remission, more likely to attend hospital, and more likely to have a clinician dissatisfied with the degree of disease control than those with UC on standard doses of vedolizumab (Gisbert et al. Curr Med Res Opin. 2023;39:1205-14).

8.28. The Committee noted that New Zealand people were not included in the reports and trials for vedolizumab for IBD, however, there were Australian participants. The Committee considered that the reported rates and responses following dose escalation for PNR and SLOR were likely applicable to the New Zealand population eligible to access vedolizumab.

8.29. The Committee considered that there remains insufficient evidence for blood drug concentration monitoring to guide vedolizumab dosing for effective disease control.

8.30. The Committee considered that there was little evidence for subsequent dose de-escalation of vedolizumab from Q4W to Q8W. The Committee was made aware of one paper reporting that this occurred in 15% (eight of 55) of previously escalated vedolizumab patients and none of these patients subsequently required re-escalation (Pepijn et al, Eur. J. Gastroenterol. Hepatol. 2022;34:488-95). Members considered that the criteria to de-escalate would be stringent, likely requiring excellent clinical and mucosal disease control, with or without supratherapeutic blood drug concentrations.

General

8.31. The Committee considered it reasonable to assume that people with CD who received an escalated induction dose of vedolizumab at week 10 will go on to receive Q4W dosing. The Committee further noted that the data support this for both CD and UC.

8.32. The Committee considered that those people with IBD who have PNR to vedolizumab at six weeks would opt to escalate dosing to 10- and 14-weeks. Members considered that this would be more likely to occur where blood drug concentration monitoring is available and identifies low concentrations at six weeks. However, approximately two-thirds of those receiving vedolizumab at an escalated dose frequency for PNR would not be expected to experience a response to the additional doses and would likely cease vedolizumab treatment. Members considered that this potentially futile treatment with an additional two doses presented a relatively small fiscal risk and may be clinically appropriate given that about 30% would experience treatment response.

8.33. The Committee noted the number of funding applications for IBD treatments and considered that Pharmac could seek further advice from the Gastrointestinal Advisory Committee on pharmaceutical treatments for IBD, including commentary on international guidelines and the potential treatment paradigm in New Zealand.

8.34. Members considered that consumers and/or the Consumer Advisory Committee could be informed about, and potentially provide valuable input for, applications and matters reviewed by PTAC, such as this item. Members encouraged Pharmac and PTAC to consider ways to seek and incorporate this, noting that Pharmac resource and timing within the assessment process would be important considerations.

Summary for assessment

8.35. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for vedolizumab if funding criteria for currently funded IBD indications were amended to allow for induction and maintenance dose frequency escalation. 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 Intervention	Ulcerative colitis (UC)	Crohn's disease (CD)
	Individuals receiving vedolizumab for the treatment of moderate-severe UC with either: • Primary non-response at week six, or • Secondary loss of clinical response after week six.	Individuals receiving vedolizumab for the treatment of severe CD with either: • Primary non-response at week six, or • Secondary loss of clinical response after week six.
Intervention	• *Primary non-response at week six:* Vedolizumab 300 mg at week 10 and every four weeks thereafter (if clinical response) until treatment failure or dose de-escalation. • *Secondary loss of clinical response after week six:* Vedolizumab 300 mg every four weeks until treatment failure or dose de-escalation	
Comparator(s)	*Individuals who <u>have not received</u> all other funded biologics prior to vedolizumab initiation (informed by New Zealand prescribing data and expected treatment patterns):* ○ Adalimumab – administered typically at a dose of 40 mg fortnightly, with some patients escalating to weekly adalimumab ○ Infliximab – administered typically at a dose of 5 mg/kg every eight weeks, with some patients escalating to 10 mg/kg every eight weeks ○ Ustekinumab – administered typically at a dose of 90 mg every eight weeks (no dose escalation). *Individuals who <u>have received</u> all other funded biologics prior to vedolizumab initiation:* • Continuation on standard dose vedolizumab (despite suboptimal benefit) • Best supportive care	
Outcome(s)	• Improved rates of clinical response in primary non-responders, delaying the need for subsequent lines of treatment. • Improved rates of clinical response restoration in secondary non-responders, delaying the need for subsequent lines of treatment. • Lower disease activity in later lines of treatment, associated with lower health system costs (eg hospitalisations, surgeries).	
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		

9. Esketamine - treatment resistant depression, post augmentation

Application

9.1. The Committee reviewed the application for esketamine nasal spray in the treatment of treatment-resistant depression, post augmentation.

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

Recommendation

9.3. The Committee **recommended** that esketamine for treatment-resistant depression post augmentation, be **declined**.

9.4. In making this recommendation, the Committee considered:

- The health needs of those eligible for treatment with electroconvulsive therapy (ECT) are similar to the broader population of treatment-resistant depression (TRD), previously discussed by PTAC.
- There is no clear evidence for the duration of treatment with esketamine for TRD, or guidance on when to stop treatment.
- Trials report significant placebo effects when assessing esketamine treatment for TRD; there are some negative studies, minimal data comparing esketamine with electroconvulsive therapy (ECT), and a risk of drug dependence and diversion, all of which contribute to concern regarding the use of esketamine for TRD in New Zealand.
- Suitability considerations, including requirements for healthcare professional administration and supervision and use of a calm and comfortable room for several hours, may place additive pressure on poorly resourced mental health services.
- Current cost-effectiveness evidence suggests esketamine is unlikely to be cost-effective in comparison to ECT.

Discussion

Māori impact

9.5. The Committee discussed the impact of funding esketamine nasal spray for the treatment of TRD on Māori health outcomes. The Committee noted Hauora hinengaro (mental health) is one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus.

9.6. The Committee noted the prevalence of major depressive disorder (MDD) in Māori is reported to be similar to other groups in New Zealand (Black et al. Psychiatry Res. 2017;255:128-38). The Committee considered assessment tools for MDD may be less responsive and sensitive to identifying MDD in Māori and noted the high incidence of suicide experienced by this population. The Committee also noted that Māori receive substantially fewer ECT treatments than non-Māori (New Zealand Health Survey 2018-9. MOH, 2019).

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

9.7. The Committee discussed the impact of funding esketamine nasal spray for the treatment of TRD on people who have been underserved by the health system. The Committee noted mental health issues including depression are common in refugee populations, who are known to experience health inequities (Refugee Health Care: A handbook for health professionals. MoH, 2012).

Background

9.8. In February 2020, PTAC reviewed an application for esketamine for TRD (defined in the supplier's application as "*failure of two different pharmacotherapies*"). PTAC

recommended the application be **declined** due to low strength evidence in the New Zealand clinical setting. The Committee considered that esketamine did not demonstrate a clear meaningful clinical benefit in primary outcomes combined with the short duration of trials in relation to the duration of depression. The Committee noted the uncertainty about the potential for long-term dependence and tolerance to esketamine, the absence of exit criteria or a clear clinical rationale for stopping treatment which could result in patients remaining on esketamine indefinitely. PTAC also considered there was moderate to high risk to the individual and society regarding potential misuse or diversion, despite the supplier's proposed risk management plan.

9.9. In February 2021 PTAC reviewed correspondence from the supplier regarding the funding application for esketamine for the treatment of TRD and considered the additional information did not address previous concerns regarding the application. PTAC reiterated its previous recommendation to **decline**.

9.10. In November 2020, PTAC recommended that the application for esketamine in the treatment of major depressive disorder with active suicidal ideation with intent (MDSI) be declined due to a lack of clinically relevant benefit and poor generalisability to the New Zealand context. Members considered that a majority of the concerns raised in February 2020 by the Committee in regard to the application for esketamine for treatment-resistant depression remained applicable for this application in the broader population described as having major depressive disorder with active suicidal ideation.

Health need

9.11. TRD is a type of Major Depressive Disorder (MDD) that is defined variably in the health literature, with diagnostic criteria generally ranging from between one and four antidepressant pharmacotherapies trialled but providing inadequate benefit, with or without electroconvulsive therapy (ECT). The Committee noted one generally accepted definition is "failure to respond to two trials of first-line anti-depressants of adequate duration and dose" and estimate that approximate 10-30% (up to 40%) of people with MDD, have TRD (Zaki et al. Neuropsychopharmacology. 2023;48:1225-33).

9.12. The Committee considered there is currently a lack of consensus regarding the most appropriate treatment for TRD, and many factors need to be considered as part of the decision-making process (Gabriel et al. PLoS One. 2023;18:e0281501, Taylor et al. Int J Neuropsychopharmacol. 2020;23:587-625).

9.13. The Committee noted the health needs of those with MDD and TRD were described in detail in the February 2020, and November 2020 PTAC records. The Committee considered that TRD impacts individuals' quality of life, productivity, and functioning, and also impacts the quality of life and functioning of their family and whānau. The Committee noted TRD is associated with increased risk of premature mortality (35% higher than in those with MDD without TRD) (Memon et al. Psychatr Q. 2020;91:1147-92). The Committee considered the health needs of those eligible for treatment with ECT are similar to the broader population of TRD, previously discussed by PTAC.

9.14. The Committee noted that current treatment of TRD includes antidepressants, augmentation (non-antidepressant pharmaceuticals which can have a 'depression improvement' effect), non-drug treatment (eg. cognitive behavioural therapy), and electroconvulsive therapy which is considered the gold standard treatment. The Committee noted electroconvulsive therapy is given in 'bursts' of 6-12 treatments, and remission occurs in 50-70% of people treated with ECT (Memon et al. Psychatr Q. 2020;91:1147-92). The Committee considered that ECT is resource intensive and requires a general anaesthetic. The Committee considered that the treatment process for TRD can take place over many months and years and can oscillate across the various treatment options over time.

9.15. The Committee noted an audit of psychiatry physicians in New Zealand, which surveyed their views of access to psychiatric care across the country (Every-Palmer. Aust N Z J Psychiatr. 2024;58:82-91). The Committee noted almost all respondents felt psychiatry was underfunded and under-resourced in New Zealand.

9.16. The Committee noted the prevalence of MDD in Māori is estimated to be similar to other groups in New Zealand (Black et al. Psychiatry Res. 2017;255:128-38). The Committee considered this unexpected, as Māori have higher rates of engagement with mental health services, but this rate of MDD is similar to other indigenous populations internationally. The Committee considered the reason/s for similar-appearing prevalence are unclear and considered that the assessment tools for MDD may not be accurate for capturing MDD in Māori. The Committee noted Māori receive substantially fewer ECT treatments than non-Māori (New Zealand Health Survey 2018-9. MOH, 2019; table 49 in data at Mental Health and Addiction: Service Use 2019/20 tables. MOH, 2021). The Committee noted that Māori experience inequitable outcomes for other mental health conditions in New Zealand, such as schizophrenia (Grattan et al. chizophr Bull. 2024;50:89-95).

9.17. The Committee noted mental health issues including depression are common in refugee populations, who are known to experience health inequities (Refugee Health Care: A handbook for health professionals. MoH, 2012).

Health benefit

9.18. The Committee noted that esketamine is the S-enantiomer of ketamine and is a nonselective, non-competitive, antagonist of the N-methyl-D-aspartate receptor. The Committee noted that the mechanism of action in TRD is uncertain and may also include action on opioid receptors. The Committee noted that Medsafe has approved esketamine for the treatment of TRD in adults.

9.19. The Committee noted that esketamine is administered by intranasal spray (in single dose devices) and the recommended dosage as per the Medsafe datasheet is 56 mg starting dose (28 mg if ≥65y), then 56 mg or 84 mg twice per week across weeks 1-4, then 56 mg or 84 mg once per week for weeks 5-8, then every 2 weeks or once per week from week 9. The Committee noted that the supplier advises patients need to be observed by a healthcare professional for two hours following every treatment to monitor for adverse events (preferably in a quiet room in a reclining chair) and that patients should not drive for 24 hours following each treatment.

9.20. The Committee noted treatment with esketamine is associated with various side effects (SEs) including nausea, vomiting, drowsiness and hallucinations. The Committee considered the effects of dissociation and increased blood pressure were of note, as these effects are the reason two-hour observation by a health professional in a quiet room is required after administration. The Committee noted that managing the effects of dissociation would require additional resource.

9.21. The Committee noted that esketamine remains not funded in several countries with similar healthcare systems to New Zealand including Australia, England/Wales, and Canada, due to uncertainty of clinical benefit, optimal dose and duration, long term safety, long term tolerance and dependence concerns, practicalities of administration and monitoring, and uncertain economic modelling. The Committee noted esketamine has been funded in Scotland in combination with an antidepressant for “adults with treatment-resistant MDD, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.”.

9.22. The Committee noted that the application specifically targets those who would otherwise receive ECT (post treatment with antidepressants and augmentation), but that most trial evidence for esketamine places it earlier in the treatment paradigm.

9.23. The Committee noted results from the TRANSFORM-2 trial, detailed in the February 2020 record. The Committee noted that the trial excluded many groups of people due to comorbidities (Popova et al. Am J Psychiatry. 2019;176:428-38), many of which are common in the New Zealand clinical setting, and thus considered results may not be truly representative of the real-world setting. The Committee noted TRANSFORM-2 reported both the esketamine and placebo groups having a reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) score Popova et al. Am J Psychiatry. 2019;176:428-38), and considered this evidence of a strong placebo effect.

9.24. The Committee noted editorials on the TRANSFORM-2 trial (Schatzberg. Am J Psychiatry. 2019;176:422-4, Tuner. Lancet Psychiatry. 2019;6:977-9), which mentioned that of the three TRANSFORM trials, only TRANSFORM-2 reported a statistically significant difference in favour of esketamine, and the treatment effect was mild. The authors noted the limitation and ineffectiveness of saline as a control, as those who experienced dissociation would know they received esketamine, and those who didn't, would know they received placebo (barring one person who experienced dissociation with saline). The Committee noted the Schatzberg commentary suggested that (in other studies) the antidepressant effect was blocked when naltrexone was administered (an opioid antagonist), indicating that perhaps a euphoric effect due to action on the opioid receptors was at least partially responsible for the antidepressant effect of esketamine. The Committee noted the author's observations that relapses within two weeks of discontinuation may be linked to opioid withdrawal, as such quick relapse is unusual when compared to other antidepressant withdrawal.

9.25. The Committee noted a similar, recent trial to TRANSFORM-2 conducted in China and the United States (Chen et al. Neuropsychiatr Dis Treat. 2023;19:693-707). The authors reported no significant difference in results between the antidepressant + esketamine, and antidepressant + placebo groups.

9.26. The Committee noted results from the SUSTAIN-3 trial, a Phase 3, open-label, long-term multicentre extension study assessing the long term safety and efficacy of esketamine for TRD (Zaki et al Neuropsychopharmacology. 2023;48:1225-33). The Committee noted the authors reported a mean duration of use of 31 months, and maintenance of remission in 46.1% of people, and considered long term treatment 'safe'. The Committee noted the study did not include any withdrawal attempt from esketamine, and considered bias risk included the fact that only people who had already received benefit from esketamine in the parent study were included in the open label extension. The Committee noted that people with psychiatric and/or medical comorbidities were excluded from the study.

9.27. The Committee noted an open label study comparing esketamine to quetiapine (augmentation) which reported esketamine was superior for the treatment of TRD (Reif et al. Engl J Med. 2023;389:1298-309). However, the Committee considered that quetiapine may not be the most efficacious augmentation therapy relative to other options and noted that augmentation is not the comparator for this application.

9.28. The Committee noted results of two meta-analyses assessing the effectiveness of esketamine for TRD, one in 2022 (Liu et al. Neuropsychiatr Dis Treat. 2022;18:2855-65) and one in 2020 (Memon et al. Psychatr Q. 2020;91:1147-92). Reported results were rapid improvement of symptoms, but authors noted study limitations such as allocation concealment problems, inconsistent dose frequency, and unclear duration of therapy.

9.29. The Committee noted there has been no direct comparison between esketamine and ECT to date, aside from identifying one abstract reviewing two trials (which were not referenced) (Basto et al. Eur Psychiatry. 2023;66(Suppl 1):S836-7). The Committee noted the authors suggested ECT may be superior to esketamine in treating MDD episodes.

9.30. The Committee considered that the evidence for esketamine for TRD included mostly short trials with many exclusion criteria. The Committee considered there is no clear

evidence for the duration of treatment, or guidance on when to stop treatment. The Committee also noted the significant placebo effect observed in trials, and benefits/risks in the elderly population are currently uncertain due to a lack of evidence in this population. The Committee considered there was risk of dependence, as well as some negative studies, and minimal data comparing esketamine versus ECT, all which contributed to concern regarding the use of esketamine for TRD in New Zealand.

Suitability

9.31. The Committee considered the requirements for administration and monitoring including healthcare professional administration and supervision, and the requirement for two hours in a calm and comfortable room, which may place additive pressure on already stretched psychiatric services, and may be burdensome for the individual and their whānau.

Cost and savings

9.32. The Committee noted results from a cost-utility analysis of TRD treatments (Zaki et al. Neuropsychopharmacology. 2023;48:1225-33) which concluded that ECT was more cost effective than esketamine, with a lower absolute cost, and a generation of more quality adjusted life years (QALYs). The Committee further noted that the cost of esketamine would need to reduce for it to be cost effective.

9.33. The Committee also noted from a cost-effectiveness study of esketamine for TRD conducted in the United States, which concluded esketamine was unlikely to be cost-effective for TRD without a significant price reduction (Ross & Soeteman DI. Psychiatr Serv. 2020;71:988-97).

9.34. The Committee considered that 250 patients per year receive ECT, but approximately 50,000 will have treatment resistant depression.

9.35. The Committee considered that the antidepressants utilised in conjunction with esketamine treatment would be agreed to on a personalised basis, dependent on individual needs. For example, some antidepressants are associated with a lower risk of sedation, cardiac side-effects, weight gain, and sexual dysfunction.

9.36. The Committee considered that non-response to esketamine would result in subsequent treatments such as ECT, varying antidepressant combinations, and augmentation trials.

9.37. The Committee considered it reasonable to assume a nurse would monitor an individual administered esketamine for 2 hours following treatment.

Funding criteria

9.38. The Committee considered that assessing response to esketamine for ongoing funding at four weeks may not be appropriate, as over 90% of people would be expected to be experiencing symptomatic benefit over this short amount of time. The Committee considered this may lead to ongoing/long term use of esketamine, without adequate attempts to withdraw.

9.39. The Committee considered that access criteria for esketamine should clearly restrict use to those for whom at least two antidepressants, as well as augmentation, have been ineffective.

Summary for assessment

9.40. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for esketamine if it were to be funded in New Zealand for treatment resistant depression. 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 treatment-resistant depression (MDD) whose depression has had a poor response to at least three prior treatments within the current depressive episode including at least two different antidepressants and augmentation therapy.
Intervention	Esketamine single-use nasal spray (28 mg in one device). • In the induction phase (weeks 1-4) the initial dose is 56 mg (two devices) twice weekly and subsequent dose of 56 mg or 84 mg twice weekly. • The maintenance phase (weeks 5-8) involves 56 mg or 84 mg esketamine once weekly. • From week 9 treatment frequency is adjusted to either every 2 weeks or once weekly. After depressive symptoms improve, treatment should continue for at least 6 months. Esketamine is intended to be administered under the direct supervision of a healthcare provider and prescribed in conjunction with a newly initiated oral antidepressant.
Comparator(s) (NZ context)	The current application is likely to have a mixed comparator depending on age: **Adults aged 65+ years** Electroconvulsive therapy (ECT) (Geduldig & Kellner. Curr Psychiatry Rep. 2016;18(4):40; Dominiak et al. Pharmaceuticals (Basel). 2021;14(6):582). **Adults aged less than 65 years** Continued use of anti-depressive treatments, based on evidence suggesting younger groups benefit less from ECT (Dominiak et al. 2021). Note that under the proposed Special Authority criteria patients must have trialled and their TRD did not respond to an SSRI and SNRI, therefore it is unclear whether these may be a comparator.
Outcome(s)	Evidence comparing esketamine against ECT in this population is not available. However, evidence for esketamine against other anti-depressants is available, as outlined below. Response: Improved time to remission, rates of remission, relapse prevention with esketamine compared to quetiapine (Reif et al. Neuropsychiatry. 2023. Poster presentation). Response to treatment (improvement of ≥50 percent in symptoms of depression on the depression rating scale, but less than the threshold for remission); remission (depression rating scale score less than or equal to a specific cutoff that defines the normal range) (Samalin et al (2023); Oral presentation at EPA, Paris France) Health-related quality of life (HRQoL): Improvements in quality of life, depression rating scores and trend in towards improvement in productivity (Hopwood et al (2023); Oral presentation at RANZCP Congress May 28 – June 1, Perth WA) Health states: If cost-utility analysis required, the following health states might be considered: - Major depressive episode - Response - Remission - Death Transitions between these health states might be informed by the publications provided above and in the supplier application.

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.

10. PDE5 inhibitors for erectile dysfunction

Application

10.1. The Committee reviewed the application for phosphodiesterase 5 inhibitors (PDE5i) for treatment of erectile dysfunction following prostate cancer treatment.

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 phosphodiesterase 5 inhibitors (PDE5i) for treatment of erectile dysfunction following prostate cancer treatment be recommended with a **high priority**, subject to Special Authority criteria.

10.4. The Committee recommended based on the following:

- The unmet health need of the population
- The impact on the quality of life of the individual and others affected
- The current health access inequity

10.5. The Committee recommended the proposed Special Authority criteria should be reviewed by a urologist specialising in the treatment of prostate cancer.

Discussion

Māori impact

10.6. The Committee discussed the impact of funding PDE5i for the treatment of erectile dysfunction following prostate cancer treatment on the Pharmac Hauora Arotahi – Māori health areas of focus and Māori health outcomes. The Committee noted that cancers detected in Māori men are more likely to be of a high grade (Gleason 8 or above), compared to those in non-Māori men (Matti et al. BJUI Int. 2020;128 Suppl 3:11-7) and are more likely to undergo radical surgical treatment for prostate cancer that could result in erectile dysfunction. In addition, the Committee noted a 2014 study that reported reduced access to treatment options for Māori men with erectile dysfunction, with Māori men experiencing considerable inequity in access to primary care, and 14% of Māori (5% non-Māori) reporting a cost barrier to collecting a prescription (Lawrenson et al. The Midlands Prostate Cancer Study: Understanding the pathways of care for men with localised prostate cancer, 2014).

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

10.7. The Committee considered that whilst there was no specific information for Pacific peoples with prostate cancer and erectile dysfunction, this population may experience

many of the same barriers to access and later diagnosis as Māori, and therefore the unmet health need was likely similar in this population.

10.8. The Committee noted there are no public hospital clinics for erectile dysfunction, nor are there any currently funded treatments for erectile dysfunction resulting from prostate cancer treatment, and individuals wishing to access PDE5i would be required to purchase them from a pharmacy (following either a prescription or a recommendation from a pharmacist), which the Committee considered would affect individuals most experiencing socioeconomic deprivation and/or a lower level of health literacy. The Committee noted Jeffreys et al. 2023 reported 10.4% of people living in an area of high deprivation (quintile 5), and 8.7% who self-reported as having a 'lower income', experience a cost barrier to being able to fill a prescription.

Background

10.9. The Committee noted it had previously considered an application for PDE5i (sildenafil, tadalafil) and/or intracavernosal alprostadil for the treatment of erectile dysfunction in people with spinal cord injury in May 2014, which received a medium priority recommendation. The Committee noted that access to sildenafil was widened to include people who have erectile dysfunction as a result of spinal cord injury in September 2019.

10.10. The Committee noted that it had previously considered that "*patients with other causes of erectile dysfunction, such as diabetes, hypertension, multiple sclerosis or damage after prostate surgery, could have a similar case for funding".*

Health need

10.11. The Committee previously noted the health need of those with erectile dysfunction after spinal cord injury in May 2014.

10.12. The Committee noted that there are multiple causes of erectile dysfunction, with age, diabetes, obesity, physical inactivity, depression, alcohol, smoking, chronic kidney disease, cardiovascular and neurological pathologies reported to be important (Bratu et al. J Med Life. 2017;10:13-8). In addition, hormonal and trauma including penile fracture, pelvic injury and colon and bladder surgery are also known to cause erectile dysfunction.

10.13. The Committee noted a variety of drugs including opioids, anticholinergics, cardiovascular agents, and tranquilisers are known to affect erectile dysfunction.

10.14. The Committee noted that many of those presenting with prostate cancer have an increased number of risk factors for erectile dysfunction prior to treatment. The Committee noted Valicenti et al. Urology. 2001;57:769-73 reported that prior to all treatments, 87% were sexually potent with 36% fully potent (having little or no difficulty with penetration at intercourse). The Committee considered that information on erectile dysfunction prior to treatment was not routinely captured in New Zealand.

10.15. The Committee noted there were approximately 4,007 new cases of prostate cancer registered in New Zealand in 2020, with 708 deaths (Te Whatu Ora, cancer web tool).

10.16. The Committee noted that there are a number of erectile dysfunction assessment tools available. The International Index of Erectile Function (IIEF-5) Questionnaire is commonly used in the assessment of erectile dysfunction, but use in New Zealand remains unknown.

10.17. The Committee noted that treatment was dependent on stage of disease, with individuals with localised prostate cancer of low or intermediate risk being treated with radical prostatectomy or radiation therapy (RT) (including external beam or seed brachytherapy). Treatments for localised disease with unfavourable intermediate or high-risk include

androgen-deprivation therapy (ADT) with a gonadotrophin-releasing hormone (GnRH) agonist, with or without an anti-androgen, in combination with RT.

10.18. The Committee noted that erectile dysfunction rates that arise from prostate cancer treatments are variable and not well characterised, with rates from radical prostatectomy varying between 14-90% (Tal et al. J Sex Med. 2009;6:2538-46).

10.19. The Committee noted that there was a delay in the presentation of erectile dysfunction from RT of approximately 8 ± 5 months after RT (Mulhall et al. J Sex Med. 2005;2:432-7).

10.20. The Committee noted that there were no clear treatment guidelines, or dedicated clinics, for the management of erectile dysfunction in New Zealand. The Committee considered that treatment of erectile dysfunction is challenging, and a multi-disciplinary approach was necessary. The Committee considered that management of the condition should include assessment before initial treatment, counselling with the partner of the individual, review of treatments and identifying any potential causes, before initiating treatment.

10.21. The Committee considered it was unknown how many individuals in New Zealand were accessing PDE5i privately following consultation with a pharmacist.

10.22. The Committee noted a survey of 546 individuals with erectile dysfunction after prostate cancer treatment, which reported that a fifth (21%) were not offered any erectile dysfunction management, and a similar proportion (23%) were not satisfied with the way healthcare professionals addressed their erectile dysfunction concerns. The survey also reported poor communication between clinicians and men, including failure to initiate discussions about erectile dysfunction and/or involve partners, with 12% of men not told that erectile dysfunction was a risk factor of prostate cancer treatment (Dyer et al. BMJ Open 2019;9:e030856).

10.23. The Committee noted Resnick et al. N Engl J Med. 2013;368:436-45, a study in 3,533 men over the course of 15 years. The study reported individuals undergoing prostatectomy were more likely to have erectile dysfunction at 2 years (odds ratio (OR) 3.46; 95% CI 1.93 to 6.17) and 5 years (OR 1.96; 95% CI 1.05 to 3.63); no significant between-group difference was noted at 15 years. The analysis also reported men treated for localised prostate cancer commonly had declines in all sexual function domains during 15 years of follow-up.

10.24. The Committee noted Nelson et al. J Sex Med. 2011;8:560-6, a study of the relationship between erectile dysfunction and depressive symptoms in 339 individuals with prostate cancer, reported, when answering the question, "I am able to have and maintain an erection" on a 1 to 5 scale (5 representing the best function), the mean score was 2 indicating "a little bit." On univariate analysis, erectile function and depression were associated, r=-0.12, P<0.05. Other variables associated with depression were marital status, r=0.11, P<0.05; anxiety scores, r=0.56, P<0.01; and social support, r=-0.42, P<0.01. On multivariate analysis, erectile function remained a significant predictor of depression, beta=-0.10, P<0.05.

10.25. The Committee noted Zaider et al. J Sex Med. 2012;9:2724-32, which reported around one-third of men assert that they have a moderate to severe loss of masculinity after treatment for localised prostate cancer.

10.26. The Committee noted Emanu et al. Curr Opin Support Palliat Care. 2016;10:102-7, which reported emotional distress can result in an avoidance in seeking, and adherence, to treatment. Of men who seek help to treat their erectile dysfunction, adherence to treatment is poor. It is estimated that 50 to 80% of men discontinue their use of erectile dysfunction treatments within a year of starting them.

10.27. The Committee noted Salonia et al. J Sex Med. 2008;5:1941-8, which reported 50% of men who were interested in seeking treatment for erectile dysfunction took steps to access treatment.

10.28. The Committee noted de Boer et al. J Sex Med. 2005;2:445-50, a study of men (non-cancer sample) who were found that have erectile dysfunction, in which 69% of men did not accept that they had erectile dysfunction and the median time to pursue treatment for erectile dysfunction was two years.

Māori health need

10.29. The Committee noted that prostate cancer diagnosed in Māori men were 73% more likely to be of a high grade compared to those in non-Māori men (Matti et al, BJUI International, 2020; 128(S3):11-17), and considered that Māori men are more likely to undergo radical treatment that would result in erectile dysfunction.

10.30. The Committee noted a 2014 study 'Understanding the pathways of care for men with localised prostate cancer' that reported within the Midlands region of New Zealand, Māori men reported more difficulty with their erectile function than non-Māori men ($p<0.01$), and the overall total was also lower for Māori men compared with non-Māori in this sample ($p<0.05$). The Committee noted the study also reported access to treatments may be reduced for Māori, with 92% not trying any of the treatment options.

10.31. The Committee also considered that some Māori men experience 'whakamā' (to be ashamed, embarrassed), which makes seeking treatment for erectile dysfunction difficult and contributes to poor health outcomes.

Health benefit

10.32. The Committee noted PDE5i causes vasodilation in the penis and lungs by blocking the breakdown of cyclic guanosine monophosphate (cGMP), which results in prolongation of the action of mediators of vasodilation including nitric oxide (NO).

10.33. The Committee noted the following studies provided by Prostate Cancer Foundation New Zealand to support the health benefit of PDE5i in the treatment of erectile dysfunction:

- Schoentgen et al. Front Surg. 2021:8:648345
- Tsertsvadze et al. Ann Intern Med. 2009;151:650-61
- Zelefsky et al. J Urol. 2014;192:868-74
- Montorsi et al. J Sex Med. 2005;2:658-67
- Ichikawa et al. Int J Urol. 2004;11:755-62
- O'Connor et al. J Health Psychol. 2012;17:3-13
- Falagario et al. J.Urology. 2022; 207

10.34. The Committee noted the following studies reporting the health benefit of sildenafil in individuals with erectile dysfunction following prostate cancer treatment:

- Kedia et al. Urology. 1999;54:308-12
- Incrocci et al. Int J Radiat Oncol Biol Phys. 2001;51:1190-5.
- Incrocci et al. Urology. 2003;62:116-20
- Harrington et al J Med Imaging Radiat Oncol. 2010;54:224-8.
- Shemtov et al. Can J Urol. 2004;11:2450-5.
- Merrick et al. Urology. 1999;53:1112-6.
- Ilic et al. J Med Imaging Radiat Oncol. 2013;57:81-8
- Bruner et al. J Sex Med. 2011;8:1228-38.
- Raina et al. Urology. 2003;62:1103-8.

- Ohebshalom et al. J Urol. 2005 ;174:258-62; discussion 262.
- Kim et al. Andrology. 2016;4:27-32
- Pavlovich et al. BJU Int. 2013 Oct;112:844-51
- Valicenti et al. Urology. 2001 ;57:769-73.
- Bannowsky et al. BJU Int. 2008;101:1279-83.
- Jo et al. J Urol. 2018;199:1600-06

10.35. The Committee noted the following studies reporting the health benefit of tadalafil in individuals with erectile dysfunction following prostate cancer treatment:

- Incrocci et al. Int J Radiat Oncol Biol Phys. 2006;66:439-44.
- Incrocci et al. Urology. 2007;70:1190-3
- Pianski et al. JAMA. 2014;311:1300-7.
- Ricardi et al. J Sex Med. 2010;7:2851-9.
- Zhang et al. Asian J Androl. 2022;24:473-77.
- Pugh et al. Brachytherapy. 2015;14:160-5.
- Canat et al. Kaohsiung J Med Sci. 2015;31:90-5.
- Montorsi et al. Eur Urol. 2014;65:587-96
- Patel et al. BMC Urol. 2015:15:31.
- Mulhall et al. J Sex Med. 2016;13:679-83
- Hirik et al. Arch Ital Urol Androl. 2016;88(4-6

10.36. The Committee noted the clinical trials had a variety of endpoints, administration regimes, with a lack of cohesive scoring systems, and different grades of erectile dysfunction in the treatment groups with different pathological groups included. The Committee considered it was therefore challenging to compare studies into the condition.

10.37. The Committee noted Goh et al. Transl Androl Urol 2022;11:124-38, a meta-analysis on the effects of PDE5i in individuals who had undergone a nerve-sparing radical prostatectomy. The authors reported '*In terms of the quality of the evidence of the outcome data, inconsistency problems were detected in all outcomes and imprecision problems in most outcomes'.*

10.38. The Committee noted many trials did not report if the participants had pre-existing erectile dysfunction. The Committee noted that many with prostate cancer may also have had erectile dysfunction prior to initiating prostate cancer treatment.

10.39. The Committee considered that many of the trials did not consider the benefits of implementation before therapy, and that the psychological, culture or religious aspects were not reviewed as part of the studies. The Committee noted Schoentgen et al. Front Surg. 2021:8:648345 reported self-confidence, therapeutic alliance, and adherence to treatment were stronger for individuals with preoperative consultations ($p < 0.05$) and erectile function recovery was better in cases of a higher number of follow-up visits (OR 4-5 visits vs. 1:12.19, $p = 0.002$).

10.40. The Committee noted some trials had a poor response rate to surveys.

10.41. The Committee noted the studies had small populations included.

10.42. The Committee considered, due to the high variability in the number of those affect by erectile dysfunction and the onset time following different prostate cancer treatments, it is difficult to assess if there was similar efficacy between prostate cancer treatment groups.

10.43. The Committee considered that optimal treatment of erectile dysfunction involves a holistic treatment plan, including mental health support and regular follow-up with the prescriber.

10.44. The Committee noted that, in the setting of prostate cancer specifically, treatment of erectile dysfunction may also include preoperative assessment of the individual's erectile function and pre-emptive treatment of erectile dysfunction while the individual is undergoing prostate cancer treatment, as well as partner involvement and counselling.

10.45. The Committee noted evidence that, for people undergoing radical prostatectomies, preoperative sexual rehabilitation was associated with improved self-confidence, therapeutic alliance, and adherence to treatment, and those who also received follow-up consultations experienced better erectile function recovery after the surgery (Schoentgen et al. 2021).

10.46. The Committee noted Ichikawa et al. Int J Urol. 2004;11:755-62, which reported results of a survey of 98 partners of individuals with erectile dysfunction, which included questions on female sexual function, where some form of sexual dysfunction affected 46.7% of the women, and a significant number (P = 0.023) of the female partners disappointed with the treatment had some kind of sexual dysfunction. The Committee considered that counselling for both partners in a relationship was important in the treatment of erectile dysfunction.

Sildenafil

10.47. The Committee considered early initiation of treatment prior to surgery may provide better health benefits. The Committee noted Jo et al. J Urol. 2018;199:1600-06 reported the proportion who achieved full recovery was significantly higher during the 12 months in the group who were treated immediately after catheter removal (early group) compared to those treated 3 months after (delayed group) (β = 0.356, p <0.001, generalised estimating equation). After 9 months postoperatively the proportion who achieved full recovery steadily increased to 41.4% at 12 months in the early group vs delayed group showed no further improvement.

10.48. The Committee noted Pavlovich et al. BJU Int. 2013;112:844-51 reported for those treated with a prostatectomy, daily dosing compared with on demand administration does not provide any significant health benefits. The study of 100 individuals reported no significant effects of treatment group (nightly vs on-demand sildenafil) on recovery of potency, as assessed by absolute IIEF-EF scores (P = 0.765), on percentage of men returning to an IIEF-EF score >21 (P = 0.830), or on IIEF-EF score recovery to a percentage of baseline value (P = 0.778).

Tadalafil

10.49. The Committee considered the health benefit of tadalafil was similar to sildenafil, however tadalafil has a longer half-life (17.5 hrs versus 4 hrs).

10.50. The Committee noted Incrocci et al. Int J Radiat Oncol Biol Phys. 2006;66:439-44 reported that in 60 individuals following RT, 67% reported improvement of erectile function, with 48% achieving successful intercourse, with tadalafil treatment; however there was minimal effect at one year.

10.51. The Committee noted Ricardi et al. J Sex Med. 2010;7:2851-9 had reported most individuals randomised experienced improved clinical outcomes when administered 20mg on-demand or 5mg on-demand tadalafil daily, with significant improvements in all domains of the IIEF for both doses (P = 0.0001), and mean erectile function domain scores values of 25 and 27.1 for the 20-mg and 5-mg tadalafil respectively (P = 0.19).

Suitability

10.52. The Committee considered individuals with potential contraindications to PDE5-i, such as ischemic heart disease, may still be able to receive a PDE5-i, starting on a reduced initial dose that increases over time to the optimal dose, which may prevent them being excluded from treatment due to contraindications. The Committee considered this might also be appropriate for individuals with consequent hypotension. The Committee considered that only a small number of people would have an absolute contraindication to the use of a PDE5i.

Cost and savings

10.53. The Committee noted that PDE5i treatment for erectile dysfunction is typically titrated to effect, with a maximum dosage of 100 mg for sildenafil and 20 mg for tadalafil. The Committee noted that between 80% to 90% of individuals may require titration to the maximal dosage (Kedia et al. Urology. 1999;54:308-12; Incrocci et al. Int J Radiat Oncol Biol Phys. 2001;51:1190-5).

10.54. The Committee considered that the number of individuals who would access funded treatment with PDE5i, if access were to be widened to people with erectile dysfunction following prostate cancer treatment, was highly uncertain due to uncertainties around the likely duration of therapy, the size of the potential eligible population, as well as a lack of data to inform likely uptake and adherence.

10.55. The Committee considered that the level of private market use of PDE5i treatment may provide some indication of the level of uptake likely to be achieved by widening access to people following prostate cancer treatment. The Committee noted however, that it was unclear how many people were currently accessing privately funded treatment specifically for prostate cancer treatment-related erectile dysfunction.

10.56. The Committee considered that uptake of publicly funded PDE5i therapy may be rapid as people currently accessing treatment through the private market could switch to having their treatment publicly funded.

10.57. The Committee considered that the intent of widening access to PDE5i therapy was to treat prostate cancer treatment-related erectile dysfunction, however there was the potential for the widespread adoption of a PDE5i among people with erectile dysfunction due to non-prostate cancer treatment-related causes. The Committee considered that use of PDE5i outside the intended target population could have a material impact on the number of people receiving funded treatment and subsequent financial impacts.

10.58. The Committee considered that some people with erectile dysfunction following prostate cancer treatment may have experienced erectile dysfunction prior to receiving prostate cancer treatment, although there was a lack of high-quality data on how many people this might involve. The Committee further considered that there was no reliable way to differentiate between prostate cancer treatment-related erectile dysfunction and erectile dysfunction following prostate cancer treatment due to non-treatment-related causes, because delayed presentations of erectile dysfunction are common.

10.59. The Committee considered that if people diagnosed with prostate cancer received PDE5i therapy to treat erectile dysfunction that is not treatment-related (eg that due to other causes such as diabetes or vascular disease), this would create a potential inconsistency in funded access to treatment, where people with erectile dysfunction due to the same causes but do not have prostate cancer do not have access to funded treatment.

10.60. The Committee considered that widening access to PDE5i may result in increased health sector costs as treated individuals may visit their prescriber more often for dose changes

and monitoring of cardiovascular effects. The Committee considered that in most cases, treatment effectiveness should be reviewed after the first eight doses.

10.61. The Committee considered that the average duration for which individuals may receive a PDE5i may be between two to ten years. The Committee noted that the treatment durations reported by trial and observational studies varied substantially for a range of reasons, and there was a lack of long term follow up data on likely persistence beyond two years.

10.62. The Committee noted a Swedish observational study, which reported that the proportions of people receiving a PDE5i rose steeply following a radical prostatectomy and that persistence on a PDE5i was relatively low at two years post-surgery (Plym et al. J Sex Med. 2014;11:2100-8). The Committee considered that for some individuals, erectile dysfunction resolves in the months following surgery and treatment with a PDE5i may not be required long term.

10.63. The Committee noted that people who have received RT for prostate cancer may experience delayed presentation of erectile dysfunction, with some studies reporting delays in onset of erectile dysfunction from RT treatment of up to two years (Wittmann et al. Int J Impot Res. 2009;2:275-84). The Committee noted observational evidence that the proportions of people on medications for erectile dysfunction following RT increased slowly over time, which was consistent with individuals experiencing delayed presentations (Plym et al. 2014).

10.64. The Committee noted an open-label extension to a randomised trial, which reported that among trial participants treated for erectile dysfunction following external beam RT, persistence on sildenafil was 24% after two years (Incrocci et al. Urology. 2003;62:116-20). The Committee also noted an observational study that reported that among people who had received RT for prostate cancer and were receiving sildenafil four years after RT, 74% of participants experienced a response to sildenafil, with a mean total IIEF-5 score of 18.3 ± 1.2 (Raina et al. Urology. 2003;62:1103-8).

Funding criteria

10.65. The Committee considered the proposed Special Authority criteria should be reviewed by a urologist.

10.66. The Committee considered that it may be appropriate for individuals to trial up to eight doses before surgery to determine the level of treatment response to PDE5i prior to prostate cancer treatment. The Committee considered treatment would not be continued in those who did not experience a good response to the treatment. The Committee considered that the appropriateness of this approach to treatment should be reviewed by a urologist.

10.67. The Committee highlighted its previous consideration that other groups experiencing erectile dysfunction due to non-prostate cancer treatment related causes also had a substantial unmet health need. The Committee considered the effectiveness of the PDE5i in other groups had not been reviewed by the Committee.

Summary for assessment

10.68. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for PDE5i if they were to be funded in New Zealand for erectile dysfunction following prostate cancer treatment. 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 who **are undergoing or have undergone treatment of any modality for prostate cancer** and are experiencing erectile dysfunction.
Intervention	Sildenafil tablets, at a starting dose of 50mg taken approximately one hour before sexual activity. • An estimated average frequency of use of twice per week (Incrocci et al. Int J Radiat Oncol Biol Phys. 2001;51:1190-5.) • An estimated 80% of treated individuals, who experience a response to sildenafil, may require a dose escalation to 100mg (Kedia et al. Urology. 1999;54:308-12). • Taken indefinitely provided the treatment remains appropriate and the individual is benefiting from treatment. Persistence on a PDE5i estimated to be roughly 24% after two years (Incrocci et al. Urology. 2003;62:116-20)
Comparator(s) (NZ context)	No funded PDE5i treatment.
Outcome(s)	Treatment response • PDE5i treatment is associated with a higher international Index of Erectile Function – Erectile Function domain score compared to placebo, among people with erectile dysfunction following surgical treatment for prostate cancer (mean diff = 4.04, 95% CI 2.87 to 5.22) (Cui et al. Andrologia. 2016;48:20-28). • The efficacy of PDE5is is assumed to be similar between people who received different prostate cancer treatment modalities. Improved health-related quality of life • Improved erectile function, as measured by the International Index of Erectile Function, is associated with improved health-related quality of life (Smith et al. Clin Drug Investigation. 2012;25:99-105)

11. Naloxone nasal spray for opioid overdose

Application

11.1. The Committee reviewed an application for naloxone nasal spray for the treatment of opioid overdose from the New Zealand Drug Foundation.

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 naloxone nasal spray be listed with a **low priority** for use by emergency medical service personnel who both:

- currently have access to naloxone ampoules; and
- are already trained in providing intravenous and intramuscular injections.

11.4. In making this recommendation, the Committee considered:

- Paramedics in New Zealand currently carry and administer naloxone ampoules for injection, intramuscularly (IM) and intravenously (IV) as required.
- Suitability benefits of intranasal over injection formulations are lessened by expertise and familiarity of trained emergency medical services staff in giving injected naloxone.
- Currently the highest quality evidence most relevant to New Zealand suggests intranasal naloxone is inferior to intramuscular naloxone in this setting, and no robust evidence comparing intranasal naloxone to titrated intravenous naloxone is available.
- Avoiding needle-stick injuries is a suitability benefit of intranasal naloxone, but this is not currently supported by empirical evidence in this setting.
- A significant proportion of IM and IV naloxone use might be expected to be replaced by an intranasal formulation if it were to be funded in this setting.

11.5. The Committee **recommended** that naloxone nasal spray be listed for use by non-paramedic first responders (ie fire service, police) with a **high priority**.

11.6. In making this recommendation, the Committee considered:

- First responders other than paramedics (eg. police, fire service) are often the first to attend emergencies, including opioid overdoses, particularly in rural settings
- Most non-medical first responders will have limited, or no familiarity and expertise, with giving IM/IV injections.
- Intranasal naloxone will be associated with lesser training requirements than IM/IV naloxone for non-paramedic first responders.

11.7. The Committee **recommended** that naloxone nasal spray be listed for individuals at high risk of opioid overdose, as part of a take-home naloxone (THN) programme, with an accompanying built-in education and support program, with a **high priority**.

11.8. In making this recommendation, the Committee considered:

- Many different populations are at increased risk of opioid overdose, and that there is significant overlap of people included in these various populations.
- Results from international THN pilot programmes have indicated success in its use for reversal of opioid overdoses, and a likely reduction in overdose deaths.
- Results of the Australian pilot programme indicated there to be a preference for intranasal over intramuscular naloxone administration in the THN setting, though a small proportion preferred prefilled intramuscular naloxone syringes
- It would be reasonable to pilot and evaluate a programme in both rural and urban settings where there is evidence of a high health need from opioid overdose, to identify the population who may use THN, explore the benefit of THN in New Zealand, and help initially assess any other impacts of the intervention.

Discussion

Māori impact

11.9. The Committee discussed the impact of funding naloxone nasal spray for the treatment of opioid overdose on Māori health outcomes. The Committee noted Hauora hinengaro (mental health) is one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus.

11.10. The Committee noted Māori are disproportionately affected by harm from substance use disorder and unspecified fatal substance overdose in New Zealand (New Zealand Drug

Foundation, 2022). The Committee noted inequitable harm for Māori caused by opioid overdose in New Zealand echoes international data from Canada, which reported indigenous populations were significantly more impacted by opioid overdose and death compared to many other populations (Lavalley et al. CMAJ. 2018;190:E1466-7).

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

11.11. The Committee discussed the impact of funding naloxone nasal spray for the treatment of opioid overdose on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted a recent retrospective analysis of naloxone use by New Zealand emergency medical services (EMS) from 2017-2021 that reported areas experiencing greater socioeconomic deprivation comprised a higher proportion of naloxone administration events in New Zealand (Kumpula et al. Emerg Med Australas. 2023).

11.12. The Committee noted the State of the Nation 2022 report produced by the New Zealand Drug Foundation conveyed that Pacific peoples and people living in socio-economic deprivation are more likely to experience harm from alcohol or substance use (including from opioids) and are more likely to want help with their substance use, but not receive it. Coronial data, as well as naloxone administration event data from Kumpula et al. 2023 did not suggest Pacific peoples have disproportionately high rates of overdose, though there are limitations in these data sources.

11.13. The Committee considered that people living in rural areas in New Zealand often experience longer wait times and reduced access to ambulance services compared to people living in urban areas, leading to inequitable access to naloxone currently administered by paramedics.

Background

11.14. The Committee noted Naloxone hydrochloride 400 mcg/1 ml ampoules are listed on the Hospital Medicines list (HML). The Committee noted in March 2013, the Hospital Pharmaceutical Subcommittee noted Naloxone hydrochloride 400 mcg/1 ml pre-filled syringes were not subsidised and not widely used in District Health Board (DHB) hospitals, and recommended they should not be included in a national preferred medicines list (PML). The Committee noted the pre-filled syringes remain unlisted on the Pharmaceutical Schedule. Members considered these may be helpful to reduce time-to-injection.

11.15. The Committee noted that in December 2023, Pharmac announced funding of naloxone hydrochloride 400 mcg/1 ml ampoules for needle exchange services to provide naloxone containing overdose kits where they are required in the community.

Health need

11.16. The Committee noted that as per the World Health Organization (WHO), opioid overdose can be defined as exposure to an opioid compound that results in the clinical signs of depressed mental status and/or unconsciousness, slow and shallow breathing, and constricted pupils. The Committee noted that opioid-induced respiratory depression may cause cerebral hypoxia (Winstanley et al. Drug Alcohol Depend. 2021;226:108838) and if untreated, can lead to cardiorespiratory arrest and/or death (Schiller et al. Statpearls [Internet]. 2023.).

11.17. The Committee noted that the International Classification of Diseases 11th Revision (ICD-11) defines opioid dependence as “a disorder of regulation of opioid use arising from repeated or continuous use of opioids. The Committee noted a 2012 study that estimated that in New Zealand, 0.3% (9100) of people aged 15 – 64 years were dependent on

opioids (of whom half were not receiving opioid substitution therapy (OST)). However, the Committee noted the authors acknowledged that this figure was lower than previous estimates and should be considered as a minimum estimate of opioid dependence (Adamson et al. Int J Drug Policy. 2012;23:87-9).

11.18. The Committee noted that opioids were attributed to 333 deaths in New Zealand between 2017 and 2021, as per the New Zealand Drug Foundation report 'Fatal overdoses in Aotearoa 2017-2021', which cited coronial data. Regarding non-fatal opioid overdoses, the Committee noted that poisoning data in New Zealand reported over 600 people were discharged as having had opioid poisoning/non-fatal overdose in 2017/2018. The Committee considered that due to coding issues, these numbers are likely to be an undercount, and are also likely to have risen over the last few years. The Committee considered that the high numbers of death and non-fatal overdose associated with opioids indicated a high health need in those at risk of opioid overdose. The Committee noted international evidence that 46-92% of people who use opioids illicitly have experienced a non-fatal overdose, or have witnessed an overdose during their lifetime (Winstanley et al. Addict Behav, 2020;100:106027, Bennett et al. J Urban Health. 2011;88:1020-30, Doe-Simkins et al. Am J Public Health. 2009;99:788-91).

11.19. The Committee noted a retrospective analysis of naloxone use by New Zealand emergency medical services (EMS) from 2017-2021 (Kumpula et al. 2023). The Committee noted 2018 people were identified as having received naloxone over the 5-year period, of whom 468 exhibited clear response to naloxone treatment. The Committee considered that the apparently low response rate to naloxone was likely due to many people being treated with naloxone who were not experiencing an actual opioid overdose.

11.20. The Committee considered that the proportions of fatal and non-fatal opioid overdose in New Zealand is unknown, but noted an Australian estimate for heroin overdose to be 20-30 non-fatal overdoses for every fatal overdose (Drake et al. Addiction. 2003;98:1169-71).

11.21. The Committee considered that many different populations are at increased risk of opioid overdose, and that there is significant overlap of people included in these various populations. The Committee considered these populations include (but are not limited to):

- People who use prescription opioids
- People who use any illicit opioids
- People who use any illicit substances (due to the risk of adulteration with opioids)
- People with illnesses at high risk of suicide
- People with illnesses at risk of accidental overdose
- Accidental exposures (eg. children in households with opioids)
- Festival exposures and mass adulteration incidents

11.22. The Committee noted Māori are disproportionately affected by substance harm and unspecified fatal substance overdose in New Zealand, comprising 27% of the total completed coronial investigations between 2017-2021 and 25% of all deaths (New Zealand Drug Foundation, 2022), despite comprising approximately 15% of the general overall New Zealand population over this time. The Committee noted a recent retrospective analysis of naloxone use by New Zealand EMS from 2017-2021 which reported the proportion of people who were administered naloxone and who were Māori was greater than their proportion of the general New Zealand population (23% vs. 17%) (Kumpula et al. 2023).

11.23. The Committee noted Kumpula et al. reported more deprived areas comprised a higher proportion of naloxone administration events in New Zealand from 2017-2021, with 32%

of events occurring in NZDep2018 index quintile 5 (most deprived) areas, and 26%, 19%, 13% and 10% in quintile areas 4, 3, 2 and 1 respectively.

11.24. The Committee noted the State of the Nation 2022 report produced by the New Zealand Drug Foundation conveyed that Pacific peoples and people experiencing socio-economic deprivation (eg people who are homeless, people living in temporary and emergency accommodation) are more likely to experience harm from alcohol or substance use (including from opioids) and are more likely to want help with their substance use, but not receive it. The Committee noted however that Coronial data, as well as naloxone administration event data from Kumpula et al. did not suggest Pacific peoples have disproportionately high rates of overdose, though there are limitations in these data sources.

11.25. The Committee considered that those living in rural areas in New Zealand often experience longer wait times and reduced access to ambulance services compared to people living in urban areas. The Committee considered this may lead to inequitable access to naloxone currently administered by paramedics, but not by other emergency services (eg the NZ fire service).

11.26. The Committee considered that people at high risk of opioid overdose are often subjected to stigma, which can impact upon the clinical care they receive.

11.27. The Committee considered that people using methadone for OST are likely to be at higher risk of death from overdose than those who use sublingual buprenorphine with naloxone. The Committee noted numbers of people on OST treatment in New Zealand from 2014/15 to 2020/21 sourced from an annual report on mental health and addiction services (Ministry of Health, 2022). The Committee noted approximately four times the number of people were using methadone in 2020/21, in comparison to buprenorphine/naloxone (i.e. an 80:20 split methadone to buprenorphine/naloxone). The Committee considered that increase in the use of buprenorphine/naloxone in this setting (compared to methadone) may help to decrease the risk of overdose in this population.

11.28. The Committee noted that as per the Te Whatu Ora Pharmaceutical Data Web Tool, an estimated 750,000 people use prescription opioids in New Zealand outside of hospital settings, with an increase in opioid prescriptions between 2016 and 2020 (6.1% tramadol, 9% codeine, 3.5% oxycodone). Regarding the use of illicit opioids, the 2021/22 New Zealand Health Survey reported a prevalence of 1.2% of the population (approximately 49,000) for illicit opioid use over the 12 months.

11.29. The Committee considered the health needs of people who experience non-fatal opioid overdoses is uncertain. The Committee considered there is a high probability that opioid overdose can cause longstanding neurocognitive impairment and brain abnormalities, but the proportions of people experiencing these effects, the severity of the impacts and the frequency of events are unknown (Winstanley et al. Drug Alcohol Depend. 2021;226:108838). The Committee considered there are likely individuals who experience these impacts and who currently do not receive any care so are not included in any reporting about overdose events. The Committee considered that the health needs of whānau who care for brain-injured individuals following non-fatal opioid overdose is uncertain, but intuitively high.

11.30. The Committee considered that whānau of those who experience opioid overdose have differing needs if the overdose is fatal or non-fatal, and if they are aware of the person's opioid use. The Committee considered there is a clear need for psychological support for people who lose a loved one to an overdose (da Silva et al. J Psychoactive Drugs. 2007;39:301-6). The Committee considered that concern around criminal liability also affects people who witness an overdose. The Committee considered that healthcare workers mays also require psychological support following attendance at an overdose death.

Health benefit

11.31. The Committee noted that naloxone nasal spray is an opioid antagonist that acts competitively at opioid receptors, following absorption via the nasal mucosa (Wermeling. Drug Deliv Transl Res. 2013;3:63-74). The Committee noted that as per the Medsafe Datasheet for the ampoules for injection, naloxone has a half-life of 30-81 minutes, and provides reversal of opioid overdose for 30-90 minutes. The Committee noted that naloxone may precipitate withdrawal symptoms if used in people who have physical dependence on opioids. The Committee noted that post-treatment agitation is commonly experienced by people who receive naloxone (Medsafe Datasheet).

11.32. The Committee noted international media reports of "yo-yoing" between opioids and naloxone, and "Lazarus parties" where naloxone was reportedly misused. The Committee noted that these reports have been shown to be fictitious, and these practices are not prevalent in the community (Crabtree et al. BMC Public Health. 2019;19:670).

11.33. The Committee noted results of an open-label randomised five-way crossover pharmacokinetic study (*N*=38) estimating pharmacokinetic profiles of intranasal naloxone, comparing early systemic exposure with intranasal versus intramuscular naloxone, and estimating intranasal bioavailability (McDonald et al. Addiction. 2018;113:484-93). The Committee noted no severe adverse effects (AEs) were reported. The Committee considered there were limitations with extrapolating the pharmacokinetics of the population in that study to someone experiencing an opioid overdose.

11.34. The Committee noted results from randomised controlled trial comparing the effectiveness of 2 mg intranasal naloxone (*n*=83) to 2 mg intramuscular naloxone (*n*=89) for suspected opiate overdose (Kerr et al. Addiction. 2009;104:2067-74). The Committee noted that the concentration of intranasal naloxone given (intranasal 2mg/1mL spray) was much more dilute than the product currently available for purchase in New Zealand (intranasal 1.8 mg/0.1mL spray) which may impact upon mucosal absorption and thus, effectiveness. The Committee noted that adequate response was reached in 72% of the intranasal group and 77.5% in the intramuscular group [95% confidence interval (CI) -18.2 to 7.7]. The Committee noted a rescue dose of 0.8 mg IM naloxone was given after 10 minutes in fewer patients who received intramuscular naloxone (intranasal: 18.1%; intramuscular: 4.5%) (difference: 13.6%, 95% CI 4.2-22.9). The Committee noted similar rates of agitation/violence across both groups. The Committee considered that the study likely included a significant minority of people who were not experiencing an opioid overdose, as non-response in 22.5% of participants who received 2 mg intramuscular naloxone seems highly unlikely in a population truly experiencing opioid overdose and does not align with international evidence.

11.35. The Committee considered limitations of the Kerr et al. study included a higher IM dose than what would be regularly administered in New Zealand, an extended wait time before giving rescue naloxone (10 minutes), which the committee considered longer than would be expected in a real-world administration setting by both healthcare providers and in a take-home naloxone setting, and poor blinding (ie people aware if receiving IN vs IM).

11.36. The Committee noted results from a randomised, controlled, double-dummy, blinded, non-inferiority trial comparing 1.26 mg intranasal (*n*=139) and 0.8 mg intramuscular (*n*=147) naloxone (Skulberg et al. Addiction. 2022;117:1658-67). The Committee noted that the population had a Glasgow Coma Scale (GCS) of <12 and a respiratory rate (RR) <8, and considered these characteristics aligned to what might be observed among eligible people in New Zealand. The Committee noted adequate response to a single dose occurred for 105 people (97.2%) in the intramuscular group and 74 people (79.6%) in the intranasal group, and the risk of receiving additional naloxone was 19.4% (95% CI, 9.0%-29.7%) higher in the intranasal group. The Committee considered post-hoc analysis in the safety setting suggested a borderline significant lower risk of withdrawal in the intranasal group. The Committee considered this study superior to Kerr et al. when assessing efficacy of

naloxone nasal spray, due to the better blinding in the trial, a nasal spray dilution similar to the product currently available for purchase in NZ, a higher IM reversal rate than in the Kerr et al. study (suggesting a higher proportion of recipients actually suffered from an opiate overdose) and dosing of IN and IM naloxone more comparable to NZ real world practice.

11.37. The Committee considered that in New Zealand, most people receive titrated intravenous naloxone, but most comparator studies for intranasal naloxone are against intramuscular naloxone. The Committee noted results of a small randomised clinical trial conducted in Iran comparing the effects of 0.4 mg in 2 ml intranasal vs 0.4 mg (untitrated) intravenous naloxone in people with suspected opioid overdose (*N*=100) (Sabzghabaee et al. Arch Med Sci. 2014;10:309-14). The Committee considered both routes of naloxone exhibited similar efficacy, noting the only dissimilar outcome was agitation – which did not occur in any people who received intranasal naloxone, but occurred in 12 people who received naloxone intravenously. The Committee considered this may have been due to the high IV dose and non-titration of IV naloxone.

11.38. The Committee considered there was limited evidence exploring the efficacy and doses required for naloxone for opioid overdose with involvement of fentanyl, and novel potent opioids (eg nitazenes).

11.38.1. The Committee noted a 2020 systematic review indicating that overdoses with involvement of fentanyl / novel potent opioids require higher initial and cumulative doses of naloxone (Moe et al. CJEM. 2020;22:178-86).

11.38.2. The Committee noted an observational study which compared response to naloxone in people presenting with opioid overdose who later tested positive for fentanyl or novel potent opioids (Amaducci et al. JAMA Netw Open. 2023;6:e2331264). The Committee noted that two people who tested positive for the novel potent opioid 'metonitazene' presented in cardiac arrest; one died despite 6 mg naloxone, and the other survived after a total of 10 mg naloxone.

11.38.3. The Committee considered this was evidence for the high risk associated with some novel potent opioids. The Committee noted information on nitazene management published by the New Zealand Poisons Centre.

11.39. The Committee considered that in the context of EMS providing naloxone, efficacy of intranasal is likely similar to injected naloxone from a "patient-oriented outcome perspective", although higher doses of intranasal naloxone are required. The Committee considered the highest quality available evidence most relevant to New Zealand suggests intranasal naloxone is inferior to intramuscular naloxone in an EMS setting for the outcome of adequate reversal. The Committee noted no robust randomised clinical trial evidence is available comparing intranasal naloxone to titrated intravenous naloxone. However, the Committee considered current clinical best practice in New Zealand is to use titrated intravenous naloxone when IV access is attainable.

11.40. The Committee noted results from a before-and-after observational evaluation of a large-scale Swedish take-home intranasal naloxone programme from mid-2018, which reported a decrease in overdose deaths from 3.9 per 100,000 to 2.8 per 100,000 (relative reduction of 28%). However, the Committee noted this programme-associated reduction was apparent only in men, with no reduction for women (Håkansson et al. BMJ Open 2024;14:e074152).

11.41. The Committee noted the Evaluation of the Pharmaceutical Benefits Scheme Subsidised Take Home Naloxone Pilot in Australia, where THN was provided via pharmacies, specialist alcohol and other drug (AOD) services, justice and correction settings, and general health services such as hospitals (85% of provided THN was the intranasal formulation). The Committee noted the evaluation reported that the pilot enabled at least

1,649 overdose reversals between December 2019 and June 2021, the equivalent of three reversals per day. The Committee considered that it would be important to look further at this pilot, in any further assessment of the proposal for take home naloxone in New Zealand.

11.42. The Committee also noted other indirect evidence of intranasal naloxone benefit supplied by the applicant (Chimbar et al. J Addict Nurs. 2018;29:167-71).

11.43. The Committee considered that access to THN was unlikely to increase risky use of opioids or other illicit substances (Bazazi et al. J Health Care Poor Underserved. 2010;21:1108-13, Tse et al. In J Drug Policy. 2022:100:103513).

Suitability

11.44. The Committee considered that in the take home naloxone setting, survey and market data including the Take Home Naloxone Pilot in Australia, has indicated a preference for intranasal over intramuscular naloxone.

11.45. The Committee considered there may be less stigma for people associated with carrying a nasal spray than injecting equipment.

11.46. The Committee considered intranasal naloxone will mean less training would be required for first responders who do not currently carry naloxone (ie fire service, police). The Committee considered that avoiding needlestick injuries and reduced agitation may be suitability benefits for intranasal naloxone in the EMS setting, but suggested Pharmac gain further insight from ambulance services on these risks if appropriate.

Cost and savings

11.47. The Committee considered that when assessing the costs and savings of naloxone, the population could be split to include emergency medical services (EMS) as one population (including both paramedics and first responders), and people utilising take home naloxone (THN) as another population.

11.48. The Committee considered that the number of people in the THN population is difficult to estimate due to the uncertainty and overlap of various different groups at increased risk of opioid overdose. The Committee considered that extrapolating from the number of people who received treatment in the Australian pilot, based on the relative total population sizes in New Zealand and Australia, may best gauge the numbers involved. However, the Committee considered that the cost and number of users of a THN programme would be inestimable with any certainty without a programme being piloted in New Zealand in both a rural and urban setting. The Committee considered that such a pilot would also inform the use of treatment and health sector resources, and health benefits that could be anticipated from a national programme in New Zealand.

11.49. The Committee considered that in the context of use by EMS, close to 100% of intramuscular naloxone use would be replaced by an intranasal formulation if it were to be funded, whereas a much lower proportion of intravenous use would be displaced. The Committee considered that among first responders who currently do not have access to any naloxone, it was reasonable to expect that intranasal naloxone would be used exclusively. The Committee considered that in the THN setting, it would be reasonable to estimate that approximately 85% of naloxone use would be intranasal, and 15% intramuscular, in accordance with the ratios reported from the Australian THN pilot programme.

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 naloxone nasal spray if it were to be funded in New Zealand for opioid overdose. 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	The applicant has indicated a wide range of people who may receive treatment in different settings. Groups may include: • People who use opioid substitution treatment (OST) • People who have opioid dependence but are not currently receiving OST • People who use opioids at all • People who use any illicit substance • Others with substance addiction		
	People who are believed to have an opioid overdose who are being treated by emergency medical responders (clinically-trained / experienced paramedics and emergency clinicians). This group would be similar in size to the number of people currently treated with IM or IV naloxone in emergency settings.	People who are believed to have an opioid overdose who are being treated by first responders (ie NZ Fire Service, NZ Police). The size of this group is hard to estimate but may be informed by evidence from or communication with the NZ Fire Service and/or NZ Police.	People who are at high risk of opioid overdose, and may be administered intranasal naloxone as part of a take home programme by themselves, their family or friends or acquaintances. The number of people who may take up THN may only be reasonably estimated robustly via a New Zealand-based pilot programme.
Intervention	IN naloxone - 1-2 units required per overdose event to achieve adequate revival (Skulberg et al., 2022) - IN naloxone has a shelf life of 30 months An ED attendance and ambulance transport will be required after administration of the first dose. In Kumpula et al. 2023, it was reported that 97% of people were transported to the hospital.		
Comparator(s) (NZ context)	IM naloxone* 0.8 mg (Skulberg et al. 2022) An ED attendance and ambulance transport will be required after administration of the first dose. In Kumpula et al. 2023, it was reported that 97% of people were transported to the hospital.	No current naloxone ED attendance and ambulance transport, which may include airway management.	No current naloxone For some people: ED attendance and ambulance transport, which may include airway management. For others: no current health care will be received to manage the overdose.
Outcome(s)	Comparable efficacy to IM naloxone.	Improved survival of overdose events. Improved rates of adequate opioid reversal within 10 minutes, which may be a surrogate for reduced neurocognitive impairment outcomes, although evidence is limited to inform this. For people using THN, utilisation of provided THN and resupply rates may be proxies for benefits from opioid reversal (survival and reduced long term impact).	

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 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.

12. Faricimab for the second-line treatment of patients with diabetic macular oedema (DMO)

Application

12.1. The Committee reviewed the application for faricimab for the treatment of diabetic macular oedema (DMO).

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 **faricimab** be listed as **cost neutral to aflibercept** for the second line treatment of DMO subject to the following Special Authority criteria:

Initial application — diabetic macular oedema

All of the following:

1. Patient has centre involving diabetic macular oedema (DMO), and
2. Patient's disease is nonresponsive 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 micrometres; and
5. There is no centre-involving sub-retinal fibrosis or foveal atrophy; and
6. Patient has not previously been treated with aflibercept for longer than 3 months

Renewal — diabetic macular oedema

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, and
5. After each consecutive 12 months treatment with (2nd line anti-VEGF agent), patient has retried at least one injection of bevacizumab and has experienced no response.

12.4. The Committee made this recommendation based on:

- The clinical evidence demonstrating faricimab to have non-inferiority in regard to best corrected visual acuity (BSVA) to aflibercept.

12.5. The Committee requested that Pharmac staff seek advice from the Ophthalmology Advisory Committee on:

- the treatment paradigm, including the dosing schedule, for aflibercept for the treatment of DMO in New Zealand.
- whether 12-or 16-week faricimab dosing intervals would be used in New Zealand and the impact this would have for people currently being treated, people waiting to receive treatment, and on the health system.
- whether the funding of faricimab would alleviate the burden on Ophthalmology services.
- estimated likely uptake of treatment.

Discussion

Māori impact

12.6. The Committee discussed the impact of funding faricimab for the treatment of DMO on Māori health areas of focus and Māori health outcomes. The Committee noted that Matehuka (Diabetes) is one of Pharmac's Hauora Arotahi - Māori health area of focus. The prevalence of diabetes is higher and risk of diabetes related complications are greater among Māori compared to New Zealand Europeans and other ethnicities (excluding Pacific peoples and Indian peoples).

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

12.7. The Committee discussed the impact of DMO on Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations who have been underserved by the health system and the health outcomes of these populations.

12.8. The Committee noted that the prevalence of diabetes is higher among Pacific peoples and Indian peoples compared to Māori, European and other ethnicities. The Committee noted the prevalence of diabetes is also higher among Indian population groups compared to Māori and European and other ethnicities.

12.9. The Committee noted that people living in areas of the greatest level of socio-economic deprivation in New Zealand also experience higher rates of diabetes compared to people living in the lowest level of socio-economic deprivation in New Zealand. The Committee considered people in rural communities or individuals unable to access transportation would experience greater difficulty getting to their treatment appointments.

Background

12.10. The Committee noted the previous clinical considerations for treatments of DMO:

Pharmaceutical Application	Clinical Advice	Listed
Aflibercept – DMO, first-line	Recommended for declined by PTAC November 2015 and Ophthalmology Subcommittee Februnary 2016.	
Aflibercept – DMO, second line	Recommended to be listed with high priority by the Ophthalmology Subcommittee February 2016	Listed on the Pharmaceutical schedule for community and hospital use 1 June 2018.
Dexamethasone implant, DMO, first-line	Recommended to be declined by Ophthalmology Subcommittee February 2016	

Dexamethasone implant, second line, post-surgery	Recommended to be listed with medium priority by the Ophthalmology Subcommittee February 2016	Listed on the Pharmaceutical schedule for hospital use October 2017
Dexamethasone implant, second line, in pregnant women	Recommended to be listed with high priority by the Ophthalmology Subcommittee February 2016	Listed on the Pharmaceutical schedule for hospital use October 2017
Ranibizumab – DMO, second line	Recommended to be listed on the HML with low priority by PTAC May 2017	

Health need

12.11. The Committee noted that in diabetes, elevated blood glucose levels 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;5:143-55).

12.12. The Committee noted that clinical DMO is defined by retinal thickening within 2 DD of the fovea (macular centre), and clinically significant DMO is determined by the retinal thickening within 500 micrometres of the fovea or hard exudates within 500 micrometres of the fovea with adjacent thickening, and can occur at any stage of diabetic retinopathy (Manatū Hauora, Diabetic Retinal Screening, Grading, Monitoring and Referral Guidance. 2016). 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.

12.13. The Committee noted that sight-threatening diabetic retinopathy is largely preventable, through regular retinal screening and prompt treatment, however diabetic retinopathy is asymptomatic until the advanced stages, and then usually it is too late for effective treatment, therefore early detection and prevention are imperative (BPAC. Screening for Diabetic Retinopathy in Primary Care. 2010

12.14. The Committee noted in 2022 it was estimated that 307,400 people in Aotearoa New Zealand had diabetes (43.1 per 1000 population [95% CI: 43.0, 43.3]). (Te Whatu Ora – Health NZ, Virtual Diabetes Register. 2022). The estimated rates were 71.2 per 1000 people (95% CI: 70.6, 71.8) among Māori, 122.7 per 1000 people (95% CI: 121.5, 123.8) among Pacific peoples, 103.1 per 1000 people (95% CI 101.8,104.4) among Indian and 31.2 per 1000 people (95% 31.0, 31.3) among New Zealand European and other ethnicities.

12.15. The Committee noted that between 2021-2050, the number of people with diabetes in New Zealand is projected to increase by 77.2% (95% CI 56.6-99.3), to a total of 578,000 (502,000-646,000) people which equates to a prevalence rate of 62.8 per 1000 people (95% CI 60.4-65.3) (GBD 2021 Diabetes Collaborators. Lancet. 2023;402:203-234).

12.16. The Committee noted the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) has reported that approximately 20-25% of people with diabetes also have diabetic retinopathy (RANZCO, Position Statement: Diabetic Retinopathy and Diabetic Retinal Screening in New Zealand, 2022).

12.17. The Committee noted a meta-analysis study which reported the overall prevalence of clinically significant DMO among people with diabetes living in the Western Pacific region (including China, Australia and New Zealand) was 3.23% (95% CI 2.26-4.59) and globally 4.07% people per million (3.42-4.82) (Teo et al. Ophthalmology. 2021;128:1580-91). Extrapolating the prevalence of DMO from the Western Pacific region estimate to the New

Zealand diabetes population there may be 8,000 to 15,000 people with diabetes and clinically significant DMO in New Zealand.

12.18. The Committee noted the incidence/prevalence of diabetic retinopathy appears to be associated with the duration of diabetes. A large longitudinal study, based in the United Kingdom, reported that the incidence of sight-threatening diabetic retinopathy after five years, in people with diabetes (type 1 or 2) who had no signs of retinopathy at baseline, was 3.9%. In people who initially had mild diabetic retinopathy, 15% had developed sight threatening retinopathy by five years (Younis et al. Lancet. 2003;361:195-200).

12.19. The Committee noted risk factors that increase the likelihood of eye disease for people with diabetes include late diagnosis, unstable glycaemia, not receiving regular medical screening and not having complications treated aggressively.

12.20. The Committee noted the 2020 systematic literature review reported the considerable impact on visual functioning, which is more impaired in people with greater disease severity. Diabetic eye disease limits activities including working, driving, walking, and reading. In addition, vision loss in diabetic retinopathy has the potential to negatively impact psychological well-being (Cooper et al. Diabet Med. 2020;37:924-33, Spooner et al. Diabetes Metab Syndr Obes. 2019:12:1913-21).

12.21. People with DMO receiving anti-VEGF treatment have indicated ocular injections are a source of fear, stress and anxiety, and indicated that a reduction in the frequency of injections and appointments would provide health benefit (Sivaprasad et al. Clin Ophthalmol. 2016:10:939-46, Spooner et al. Diabetes Metab Syndr Obes. 2019:12:1913-1921).

12.22. The Committee noted that aflibercept is the only anti-VEGF available for second line treatment of DMO. Aflibercept treatment is initiated with one injection per month for five consecutive months, followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes (Aflibercept New Zealand Data Sheet. Medsafe). The Committee considered that based on this recommendation a person who is starting aflibercept treatment would expect to receive eight injections in the first 12-months of treatment.

12.23. A retrospective analysis of real-world data indicates that treatment-naïve people residing in the USA received an average 6.4 anti-VEGF injections during the first 12-months of treatment, and received less visual gains compared to people in randomised clinical trials (Ciulla et al. Br J Ophthalmol. 2021;105:216-221). The Committee requested that the Opthalmology Advisory Committee advise on the number of injections a person would receive in the current health care setting.

12.24. The Committee noted in a retrospective study between July 2006 to December 2019 including 245,844 people, (aged 15 years or above, who had attended or scheduled at least one Ministry of Health-funded diabetes eye service appointment) reported that when compared with New Zealand Europeans, Māori were approximately twice as likely to never receive diabetes eye care or to access ophthalmology clinics when referred, 10% less likely to receive biennial screening and received the fewest anti-VEGF injections when treatment was commenced. Moreover inequities in service access was also prevalent in Pacific peoples compared to New Zealand Europeans, younger and older aged people compared to those aged 50-59 years and those living in areas of higher deprivation (Silwal et al. PLoS One. 2023;18:e0285904).

12.25. The Committee noted the loss of vision for a person with DMO can have considerable impact on their family, whānau, and friends. A survey of people with DMO in Australia showed 25% of respondents reported that their condition affected their dependence on others for daily activities such as personal care, bathing, eating, and dressing (Spooner et al. Diabetes Metab Syndr Obes. 2019:12:1913-1921). In addition, people have reported

that loss of visual acuity impacts their ability to self-manage their diabetes, and therefore they find they need to rely on family, whānau and caregivers.

12.26. The impact on caregivers includes the time needed to frequently accompany individuals with DMO to clinic and treatment visits. People with diabetes with DMO use a significantly greater proportion of eye-care related visits compared with people with diabetes without DMO (86.4% vs 24.9%), and almost twice the number of total healthcare visit days (28.6 vs 16.9 days) per year (Kiss et al. Clin Ophthalmol. 2016; 10: 2443–2453).

12.27. The Committee noted that Matehuka (Diabetes) is one of Pharmac's Hauora Arotahi - Māori health area of focus. The prevalence of diabetes is 71.2 (95% CI 70.6, 71.8) people per 1000 among the Māori population (Te Whatu Ora – Health NZ, Virtual Diabetes Register. 2022 [assessed 7/12/2023]). As of 30 June 2022 the New Zealand's estimated Māori population was 892,200 (17.4 percent of national population) (StatsNZ, 2022) meaning there may be 63,500 Māori with diabetes in New Zealand. Extrapolating the prevalence of DMO from Teo et al. (2021) there may be 2,050 Māori with DMO.

12.28. Māori are at increased risk of diabetic complications compared with non-Māori, including microvascular disease (nephropathy, retinopathy and neuropathy) and long-term macrovascular outcomes (coronary artery disease, stroke and peripheral vascular disease) (Yu et al. Lancet Glob Health. 2021;9:e209-e217, Manatū Hauora. Tatu Kahukura. 2015. Harwood, M & Tipene-Leach, D. Hauroa: Māori Standards of Health IV. Te Rōpū Rangahau Hauora a Eur Pōmare. 2007,

12.29. The Committee noted the prevalence of diabetes is 122.7 (95% CI 121.5, 123.8 people per 1000 among the Pacific peoples population groups (Te Whatu Ora – Health NZ, Virtual Diabetes Register. 2022). As of 30 June 2022, New Zealand's estimated Pacific population was 381,642 (StatsNZ, 2022) meaning there may be 46,800 Pacific peoples with diabetes in New Zealand. Extrapolating the prevalence of DMO from Teo et al. (2021) there may be 1,500 Pacific peoples with DMO in New Zealand.

12.30. In a Samoan study of people with type 2 diabetes mellitus (n= 214 eyes, 107 people), 53.3% had diabetic retinopathy, and 25.2% had signs of macular oedema and 11.7% required treatment (Jeganathan et al. Ophthalmol Ther. 2017; 6: 187–194).

12.31. The Committee noted the prevalence of diabetes is 103.1 (95% CI 101.8, 104.4 people per 1000 among Indian population groups (Te Whatu Ora – Health NZ, Virtual Diabetes Register. 2022).

12.32. The prevalence of people with diabetes is 72.8 (95% CI 72.3, 73.3) per 1000 people living in areas of the greatest level of socio-economic deprivation in New Zealand, compared to 27.1 (95% CI 26.8, 27.3) per 1000 people living in areas of the lowest socio-economic deprivation in New Zealand (Te Whatu Ora – Health NZ, Virtual Diabetes Register. 2022 [assessed 7/12/2023]).

12.33. The Committee noted the Interim Government Policy Statement outlines health sector outcomes that are hoped to be achieved by health system partners (Te Whatu Ora, Te Aka Whai Ora and Manatū Hauora). Keeping people well and independent in their communities and achieving equity in health outcomes, apply to the application considered.

Health benefit

12.34. The Committee noted faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody. Faricimab binds and neutralises both VEGF-A, a key driver of neovascularisation and vascular permeability, and Ang-2, a regulator of vascular stability.

12.35. The Committee noted that faricimab is administered via intravitreal injection. Administration requires a clinic visit and treatment must be administered by a qualified clinician experienced in intravitreal injections. The recommended dose for faricimab is 6 mg (0.05 mL) every 4 weeks for the first four doses. Thereafter, treat-and-extend approach following an assessment of the individual patient's anatomic and/or visual outcomes can be used. Following the outcome of this assessment, the dosing interval may remain at every 4 weeks, or may be extended in 4 week increments up to every 16 weeks. Monitoring between the dosing visits should be scheduled based on the recipient's status and at the prescriber's clinical judgement. Ongoing treatment with faricimab should be maintained until the affected individual's vision deteriorates below 6/36 on the Snellen visual acuity score, as per the Special Authority Renewal criteria.

12.36. The Committee noted that faricimab is approved by Medsafe for the treatment of ophthalmologic indications including DMO and wAMD. The Committee noted health technology assessment agencies in Australia, Canada, Scotland and England/Wales have recommended faricimab for the treatment of DMO if it places no additional costs to health systems compared to currently funded anti-VEGF treatments.

12.37. The Committee noted the YOSEMITE and RHINE trials (Wykoff et al. Lancet. 2022;399:741-55, Wong et al. Ophthalmology. 2023 :S0161-6420(23)00933-8):

12.37.1. The Committee noted study modifications were required due to the public COVID-19 health measures. The Committee noted the trials were highly selective with a large number of participants ineligible for trial enrolment due to 'other' reasons and considered this a limitation of the study when translating it to the New Zealand setting. The Committee also noted 77-80% of participants were white.

12.37.2. The Committee noted that 75-80% of participants had not previously received an anti-VEGF treatment and considered this a limitation of the study when translating it to the New Zealand setting where bevacizumab is the only funded first-line treatment.

12.37.3. The Committee noted there the two faricimab trial arms receiving either a fixed (every 8 weeks) or an adjustable (up to 16 weeks) dosing schedule. The control arm received aflibercept on a fixed (every 8 weeks) dosing schedule.

12.37.4. The Committee noted the primary endpoint of both studies was the change in best corrected visual acuity (BCVA) (95% CI) from baseline. The Committee noted that in both trials faricimab (both adjustable and fixed arms) were non-inferior to aflibercept regarding mean change from base line for BCVA during 1-year of treatment. The Committee noted that in the 2-year follow up both studies reported that visual acuity gains were maintained and the mean changes in BCVA from baseline in the faricimab arms were comparable to aflibercept.

12.37.5. The Committee noted that 52.8% of participants were receiving faricimab every 16 weeks, 21% every 12 weeks, 15.4% every 8 weeks and 10.8% at year 1 of the YOSEMITE trial. At year 2, 60% of participants were receiving the 16-week faricimab dose, 18.1% every 12 weeks, 14.8% every 8 weeks and 7% every 4 weeks.

12.37.6. The Committee noted that 51% of participants were receiving faricimab dose every 16 weeks, 20.1% every 12 weeks, 15.6% every 8 weeks and 13.3% at year 1 of the RHINE trial. At year 2, 64.5% of participants were receiving the 16-week faricimab dose, 13.6% every 12 weeks, 11.8% every 8 weeks and 10.1% every 4 weeks.

12.38. The Committee considered the trials demonstrated faricimab could be administered with dosing intervals up to 16 weeks, however considered the design of the trial did not allow for a comparison to aflibercept used in a similar treat-and-extend regimen.

12.39. The Committee noted the following studies:

12.39.1. Rush R & Rush S. Clin Ophthalmol.2022:16:2797-2801

12.39.2. Rush RB. Clin Ophthalmol. 2023:17:2397-2403

12.39.3. Kusuhara et al. Medicina (Kaunas). 2023;59:665

12.39.4. Eter et al. Ophthalmol Sci. 2021;2:100111

12.39.5. Ishida et al. Asia Pac J Ophthalmol (Phila). 2023;12:451-459.

12.39.6. Sahni et al. Ophthalmology. 2019;126:1155-1170.

12.39.7. Watkins et al. Adv Ther. 2023;40:5204-5221

12.39.8. Takamura et al. Invest Ophthalmol Vis Sci. 2023;64:31.

12.39.9. Ohara et al. Medicina (Kaunas) . 2023;59:1125

12.40. The Committee noted there have been no clinical trials demonstrating the second line use of faricimab following first-line treatment of bevacizumab. The Committee considered a trial designed this way would be a better reflection of the New Zealand context.

12.41. The Committee considered that people with DMO who did not benefit from first line treatment VEGF treatment would likely benefit from faricimab. The Committee considered the magnitude of benefit would be comparable to aflibercept. The Committee considered there was insufficient evidence to show benefits of third-line treatment.

12.42. The Committee noted the YOSEMITE and RHINE trials approximately 79% of people in the adjustable dosing arm were able to 12- or 16-weekly dosing intervals. The Committee considered that if the treat and extend method could be used in practice to treat DMO with aflibercept the benefit to the health system of extended faricimab dosing intervals to be unclear.

12.43. The Committee considered the funding of faricimab is unlikely to improve equitable access to effective treatments as the inability to access services is likely to be the main contributor to people not receiving treatment.

12.44. The Committee requested that Pharmac staff seek advice from the Ophthalmology Advisory Committee on:

12.44.1. the treatment paradigm, including the dosing schedule, for aflibercept for the treatment of DMO in New Zealand.

12.44.2. whether 12-or 16-week faricimab dosing intervals would be used in New Zealand and the impact this would have for people currently being treated, people waiting to receive treatment, and on the health system.

12.44.3. whether the funding of faricimab would alleviate the burden on Ophthalmology services.

12.44.4. estimated likely uptake of treatment.

Suitability

12.45. The Committee noted that like currently funded anti-VEGF therapies, faricimab is administered via intravitreal injection. Administration requires a clinic visit and treatment must be administered by a qualified clinician experienced in intravitreal injections.

12.46. The Committee noted the treatment of DMO is lifelong if people are benefiting from treatment and this involves frequent visits to healthcare centres. If their eyesight is impaired, assistance with transportation to appointments may also need to be considered. The Committee noted that frequent visits to hospital are likely to have direct costs to the person and their family/whānau, and may involve taking time off work, arranging for the support of a caregiver, and travelling long distances if living rurally.

Cost and savings

12.47. The Committee considered that if faricimab were funded it would likely replace current treatment, but that further advice should be sought on uptake over time.

12.48. The Committee noted there was insufficient high-quality evidence indicating faricimab would require less frequent injection than other anti-VEGF agents (ie extended time interval between doses). The Committee noted that people will still need to be monitored in between treatment doses.

Funding criteria

12.49. The Committee noted the suppliers proposed Special Authority criteria included faricimab for third-line treatment of DMO. The Committee considered there to be limited evidence regarding the efficacy and safety of faricimab in the third line setting and recommended exclusion from the criteria.

12.50. The Committee noted the following Special Authority criteria for faricimab for the second line treatment of DMO to be appropriate.

Initial application — diabetic macular oedema

All of the following:

1. Patient has centre involving diabetic macular oedema (DMO), and
2. Patient's disease is nonresponsive 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 micrometres; and
5. There is no centre-involving sub-retinal fibrosis or foveal atrophy; and
6. Patient has not previously been treated with aflibercept for longer than 3 months

Renewal — diabetic macular oedema

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, and
5. After each consecutive 12 months treatment with (2nd line anti-VEGF agent), patient has retried at least one injection of bevacizumab and has experienced no response.

Summary for assessment

12.51. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for faricimab if it were to be funded in New Zealand for 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.

The PICO may develop based on additional clinical advice.

Population	People with DMO who do not experience therapeutic response to treatment with bevacizumab.
Intervention	Faricimab 6 mg (0.05 mL solution) every 4 weeks (monthly) for the first four 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. Bevacizumab to be retried every 12 months.
Comparator(s)	Aflibercept - further advice required on dosing schedule. Bevacizumab to be retried every 12 months.
Outcome(s)	Non-inferiority to other anti-VGEF treatments in maintaining or improving clearness or sharpness of vision in people with DMO.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

13. Faricimab for 2nd line treatment of neovascular (wet) age related macular degeneration

Application

13.1. The Committee reviewed the application for faricimab for second line treatment of neovascular (wet) age related macular degeneration (wAMD).

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

Recommendation

13.3. The Committee **recommended** that faricimab be listed as **cost neutral to aflibercept** for the second line treatment of wAMD subject to the following Special Authority criteria:

Initial application -wAMD

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 aflibercept for longer than 3 months.

Renewal criteria -wAMD

All of the following:
1. Patient is benefiting from the treatment, 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.

13.4. The Committee made this recommendation based on:

- The clinical evidence demonstrating faricimab to have non-inferiority in regard to best corrected visual acuity (BCVA) to aflibercept.
- The unclear benefit of extended treatment intervals with faricimab.

Discussion

Māori impact

13.5. The Committee discussed the impact of funding faricimab for the treatment of wAMD on Māori health areas of focus and Māori health outcomes. The Committee noted there is no evidence regarding prevalence or health outcomes among Māori with wAMD.

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

13.6. The Committee discussed the impact of wAMD on Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations who have been underserved by the health system and the health outcomes of these populations. The Committee noted there is no information reporting on the prevalence or health outcomes among these groups. The Committee considered people in rural communities or individuals unable to access transportation would experience greater difficulty getting to their treatment appointments.

Background

13.7. The Committee noted the previous considerations of anti-VEGF therapies:

13.7.1. PTAC has previously considered treatments for wAMD in 2007 (ranibizumab), 2008 (17. ranibizumab), 2015 (item 10) and 2017 (item 8).

13.7.2. Bevacizumab is listed on the hospital medicine lists and is used off label for the treatment of ocular neovascularisation or exudative ocular angiopathy.

13.7.3. Aflibercept was listed on the Pharmaceutical Schedule and Hospital Medicines list from 1 June 2018 for the second-line treatment of wAMD.

13.7.4. Ranibizumab was listed for the Hospital Medicines list from 1 June 2018 for the second-line treatment for the treatment of wAMD.

Health need

13.8. 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;232:151-64).

13.9. The Committee noted there are no direct population-based prevalence studies of AMD in New Zealand. The Committee noted extrapolated estimates from a pool-global prevalence meta-analysis reported the prevalence of 8.01% (95% CI 3.95-15.49) for early-stage AMD and 0.37% (0.18-0.77) for late stage AMD (Wong et al. Lancet Glob Health. 2014;2:e106-16). Using these estimates the prevalence of any AMD in New Zealand for the 45–85-year

age group it was estimated 7,600 people may be affected by late-stage AMD in 2014 and 8,600 being affected by 2026 (Worsley & Worsley. N Z Med J. 2015;128:44-55).

13.10. The Committee noted the prevalence of AMD among Māori and Pacific peoples is not known. Worsley et al (2015) estimated the prevalence of AMD among Māori to be zero because there were no published, or anecdotal, cases of AMD in Māori in the literature (Rapata et al. Clin Experiment Ophthalmol. 2023; 51:714-27). The common opinion among retinal specialists in Aotearoa/New Zealand is that rates of AMD are low among Māori (Rapata et al. Clin Experiment Ophthalmol. 2023; 51:714-27).

13.11. The Committee noted that between 1 July 2022 to 30 June 2023 745 people have accessed aflibercept for wAMD treatment with an initial Special Authority approval. Of those who were prescribed aflibercept, 2.8% were Māori and 1.4% were Pacific peoples.

13.12. The Committee noted the estimated prevalence of AMD in three large population-based studies was 0.2% for people aged 55-64 years and 13.1% for people more than 85 years of age. Prevalence of wAMD increased from 0.17% among people aged 55 to 64 years to 5.8% for those older than 85 years (Smith et al. Ophthalmology. 2001;108:697-704). The Committee considered that people are living longer and more people are likely to develop chronic eye conditions such as wAMD.

13.13. The Committee noted wAMD leads to irreversible central vision loss if it is left untreated. People with wAMD report experiencing blurring of their central vision, difficulty in seeing fine details, and distortion of lines and shapes (Varano et al. Clin Ophthalmol. 2016:10:257-67).

13.14. The Committee noted people with wAMD-associated visual impairment report their undertaking of day-to-day activities are affected and it changes their ability to engage in the same activities they were able to do prior to vision loss (Varano et al. Clin Ophthalmol. 2016:10:257-67). Impairment to daily living, reduced visual function and presence of any disability were associated with increased depressive symptoms among people with wAMD (Vu et al. Acta Ophthalmol. 2021;99:e547-e554).The Committee noted people can be at greater risk of accidents such as falling which can require hospitalisation (Varano et al. Clin Ophthalmol. 2016:10:257-67).

13.15. The Committee noted wAMD treatment can have considerable impact on family/whānau. Caregivers may need to take time off work or disrupt their schedules to attend injection appointments (Gohil et al. PLos One. 2015;10:e0129361, Varano et al. Clin Ophthalmol. 2016:10:257-67). The Committee noted caregivers have reported they help with treatment aftercare and day-to-day activities, and that they can experience negative emotions, including sadness (34.9%), fear (27.6%), frustration (26.8%), and depression (24.4%). However, caregivers also report feeling useful (48.4%) (Varano et al. Clin Ophthalmol. 2016:10:257-67). Contrasting this the Committee noted another study where approximately 75% of caregivers reported little or no burden associated with supporting patients with wAMD, as evaluated on the Burden Assessment Scale (Senra et al Am J Ophthalmol. 2017:177:213-224).

13.16. The Committee noted the treatment of wAMD imposes a substantial burden on healthcare providers as treatment requires a high frequency of appointments for monitoring and treatment including human resources (doctors and technicians), machines (optical coherence tomography) and examination space in hospital and clinics. These resources can be limited, and a lack of clinical capacity can result in significant delays for people requiring treatment. Te Whatu Ora has reported that ophthalmology waiting lists for (general care) first specialist appointment and procedures are large and continue to grow (3,596 waiting over four months for first specialist appointment; 3,258 waiting over four months for procedure) and that there are significant delays for care (35,748 overdue at end of May 2022, 19.2% or 6,864 of whom have waited 50% over their due date) (Reset and Restore Plan Planned Care Taskforce Te Whatu Ora. 2022

13.17. The Committee noted there is no information reporting of the health outcomes of wAMD among Māori.

13.18. The Committee noted there is no information reporting of the prevalence of wAMD among Pacific peoples, disabled people including tāngata whaikaha Māori, and other populations who have been underserved by the health system. The Committee considered people in rural communities or individuals unable to access transportation would experience greater difficulty in getting to their treatment appointments.

13.19. The Committee noted the Interim Government Policy Statement on Health outlines health sector outcomes that are hoped to be achieved by health system partners (Te Whatu Ora, Te Aka Whai Ora and Manatū Hauora). Keeping people well and independent in their communities and achieving equity in health outcomes apply to the faricimab application being considered.

Health benefit

13.20. The Committee noted faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both Ang-2 and vascular endothelial growth factor A (VEGF-A).

13.21. The Committee noted that faricimab is administered via intravitreal injection. Administration requires a clinic visit and treatment must be administered by a qualified clinician experienced in intravitreal injections. The recommended dose for faricimab is 6 mg (0.05 mL solution) every 4 weeks (monthly) for the first four doses. Thereafter, a treat-and-extend approach may be used based on the physician's judgement of the patient's anatomic and/or visual outcomes. The dosing interval may be extended up to every 16 weeks (4 months) (Faricimab New Zealand Data Sheet, MedSafe).

13.22. The Committee noted that faricimab is approved by Medsafe for the treatment of ophthalmologic indications including wAMD and DMO. The Committee noted health technology assessment agencies in Australia, Canada, Scotland and England/Wales have recommended faricimab for the treatment of wAMD if it places no additional costs to health systems compared to currently funded anti-VEGF treatments.

13.23. The Committee noted the TENAYA and LUCERNE clinical trials (Heier et al. Lancet. 2022; 399:729-740):

13.23.1. The Committee noted that no participants had previously received an anti-VEGF treatment and considered the study to be limited as these participants are not representative of the treatment population in New Zealand where bevacizumab is the only funded first-line treatment.

13.23.2. The Committee noted there were two faricimab trial arms receiving either a fixed (every 8 weeks) or an adjustable (up to 16 weeks) dosing schedule. The control arm received aflibercept on a fixed (every 8 weeks) dosing schedule.

13.23.3. The Committee noted that in both trials faricimab (both fixed and adjustable dosing schedule trial arms) were non-inferior to aflibercept regarding mean change for best corrected visual acuity (BCVA) from base line to primary endpoint visits (average of week 40, 44, 48)

13.23.4. The Committee noted that at 48 weeks over 40% of people were receiving a 16-week dosing schedule of faricimab, over 30% receiving a 12-week, the rest of the participants were receiving an 8- week dosing schedule.

13.24. The Committee considered the trials demonstrated faricimab could be administered with dosing intervals up to 16 weeks, however considered the design of the trials did not allow for a comparison to aflibercept when used in a similar treat-and-extend regimen.

13.25. The Committee noted the TRUCKEE real-world study (Khanani et al. Eye (Lond). 2023;37:3574-3581):

13.25.1. The Committee noted that 89.4% participants (337/376) were using faricimab as second line treatment and had previously received aflibercept (63%), ranibizumab (15.4%) brolucizumab (6.9%), bevacizumab (4.3%).

13.25.2. The Committee noted after one injection mean BCVA increased by +1.1 letters among all particpants, +0.2 letters for second line participants and +4.9 letters for treatment naive participants.

13.25.3. The Committee noted after three injections mean BCVA increased by +3.4 letters among all particpants, +2.7 letters for second line participants and +8.1 letters for treatment naive participants.

13.26. The Committee noted the AVENUE phase-2 clinical trial (Sahni et al. JAMA Ophthalmol. 2020;138:955-963):

13.26.1. The Committee noted that participants were treatment naive and 32-45% of participants in the trial arms had a Snellen equivalent less than 6/24.

13.26.2. The Committee noted faricimab was not superior to ranibizumab regarding mean change from baseline for BCVA.

13.27. The Committee noted the Leung et al. Clin Ophthalmol. 2023:17:1287-1293 retrospective study:

13.27.1. The Committee noted all participants had received at least three anti-VEGF injections before switching to faricimab (mean number of injections 34.2±23 anti-VEGF injections over 182.41±128 weeks).

13.27.2. The Committee noted from initial to final visit mean BCVA improved from 0.33±0.32 logMAR to 0.27±0.32 logMAR (p=0.002).

13.28. The Committee noted the following studies:

13.28.1. Khanani et al. Ophthalmol Sci. 2021;1:100076

13.28.2. Mori et al. Jpn J Ophthalmol. 2023;67:301-31

13.28.3. Khanani et al. JAMA Ophthalmol. 2020;138:964-972

13.28.4. Takahashi et al. Graefes Arch Clin Exp Ophthalmol. 2023;261:3125-3137

13.29. The Committee noted the following real-world studies:

13.29.1. Hikichi T. Jpn J Ophthalmol. 2023 Nov;67(6):652-656.

13.29.2. Rush & Rush. Clin Ophthalmol. 2022:16:4041-4046

13.29.3. Kishi et al. J Clin Med. 2023 Aug 6;12(15):5145

13.29.4. Pandit et al. Ophthalmol Retina. 2023 Oct 31:S2468-6530(23)00569-9

13.29.5. Rush RB. Clin Ophthalmol. 2023 Aug 1:17:2201-2208

13.29.6. Inoda et al. Ophthalmol Ther. 2023 Oct;12(5):2703-2712

13.29.7. Katoaka et al. Graefes Arch Clin Exp Ophthalmol. 2023

13.29.8. Grimaldi et al. Graefes Arch Clin Exp Ophthalmol. 2023

13.29.9. Mukai et al. Sci Rep. 2023 May 30;13(1):8747

13.29.10. Raimondi et al. Ophthalmol Retina. 2023 Nov 29:S2468-6530(23)00623-1.

13.29.11. Stanga et al. Eye (Lond). 2023 Oct;37(15):3282-3289

13.29.12. Szigiato et al. Ophthalmol Retina. 2024 Jan;8(1):10-17

13.29.13. Kenworthy et al. Clin Exp Ophthalmol. 2023

13.30. The Committee noted there are no clinical trials demonstrating the second-line use of faricimab following first-line treatment with bevacizumab.

13.31. The Committee considered that people with wAMD who did not receive appropriate health benefit from first line treatment would benefit from faricimab. The Committee considered the magnitude of benefit would be comparable to aflibercept. The Committee considered there was insufficient evidence to show benefits of a third-line treatment.

13.32. The Committee noted the TENAYA and LUCERNE trials approximately 79% of people in the adjustable dosing arm were able to have 12- or 16-weekly dosing intervals. The Committee noted the dosing schedule options described on the Medsafe Datasheets for Aflibercept and Ranibizumab both include the option for treat-and-extend. The Committee considered that if the treat-and-extend methods could be used in practice to treat wAMD with aflibercept or ranibizumab the incremental benefit to the health system of extended faricimab dosing intervals to be unclear.

13.33. The Committee considered the funding of faricimab is unlikely to improve equitable access to effective treatments as the inability to access services is likely to be the main contributor to people not receiving treatment.

13.34. The Committee requested that Pharmac staff seek advice from the Ophthalmology Advisory Committee on:

13.34.1. the treatment paradigm, including the dosing schedule, for aflibercept, ranibizumab, and faricimab in New Zealand.

13.34.2. whether the 12-or 16-week faricimab dosing intervals would be used in New Zealand (instead of 8-week dosing) and the consequences this would have on the health system.

13.34.3. whether the funding of faricimab would alleviate the burden on Ophthalmology services.

13.34.4. estimated likely uptake of treatment

Suitability

13.35. The Committee noted that like currently funded anti-VEGF therapies, faricimab is administered via intravitreal injection. Administration requires a clinic visit and treatment must be administered by a qualified clinician experienced in intravitreal injections.

13.36. The Committee noted the treatment of wAMD is lifelong if people are benefiting from treatment and this involves frequent visits to healthcare centres. If their eyesight is

impaired, assistance with transportation to appointments may also need to be considered. The Committee noted that frequent visits to hospital are likely to have direct costs to the person and their family/whānau, and may involve taking time off work, arranging for the support of a caregiver, and travelling long distances if living rurally.

13.37. The Committee noted that people with wAMD report the greatest barrier to treatment is the experience of the treatment itself (having to have the injections, frequency of injections, possible injection-related side effects) (Varano et al. Clin Ophthalmol. 2016:10:257-67). In another study, people with wAMD (aged 56-101) have reported travel to and from the hospital to be a significant barrier to receiving treatment (Droege et al. Graefes Arch Clin Exp Ophthalmol. 2013;251:1281-4).

Cost and savings

13.38. The Committee considered that the estimated number of people who would use faricimab if it were to be funded in New Zealand was reasonable, but that the uptake of treatment would be higher (increasing to close to 100% of people requiring second-line treatment over time). The Committee noted that the increasing elderly population would mean the population accessing treatment would likely increase over time.

13.39. The Committee noted there was insufficient high-quality evidence indicating faricimab would require less frequent injections than other anti-VEGF agents (ie extended time interval between doses). The Committee noted that people will still need to be monitored by an ophthalmologist in between treatment doses to determine treatment efficacy.

Funding criteria

13.40. The Committee noted the suppliers proposed special authority included faricimab for third-line treatment of wAMD. The Committee considered there to be limited evidence regarding the efficacy and safety of faricimab in the third-line setting and recommended exclusion from the criteria.

13.41. The Committee noted the following Special Authority for faricimab for the treatment of wAMD to be appropriate.

Initial application -wAMD

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 aflibercept for longer than 3 months.

Renewal criteria -wAMD

All of the following:
1. Patient is benefiting from the treatment, 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.

Summary for assessment

13.42. The Committee considered that the table below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for faricimab if it were to be funded in New Zealand for wAMD. 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 wAMD who have tried and have not experienced a satisfactory response with bevacizumab, or who have developed severe endophthalmitis or severe posterior uveitis following treatment with bevacizumab.
Intervention	Faricimab 6 mg (0.05 mL solution) every 4 weeks (monthly) for the first four 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.
Comparator(s)	Aflibercept – further advice required on dosing schedule. Ranibizumab - further advice required on dosing schedule.
Outcome(s)	Non-inferiority to other anti-VEGF treatments in maintaining or improving clearness or sharpness of vision in people with wAMD.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	