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 August 2025

**This meeting was held via Microsoft Teams**

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## 1. Attendance

**PTAC members:**
Rhiannon Braund (Acting 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

**Observers – Invited Experts for part of the meeting**
Dr Ravi Suppiah
Dr Vicki Quincey

## 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 |
|---|---|---|
| 10.3 | Fremanezumab for people experiencing chronic migraine, subject to Special Authority criteria | High Priority |
| 10.4 | Fremanezumab for people experiencing episodic migraine, subject to Special Authority criteria | High Priority |

| | | |
|---|---|---|
| 11.3 | Tirzepatide for people with type 2 diabetes mellitus, whose blood sugar is high despite other treatments, subject to Special Authority criteria | Medium Priority |
| 13.4 | Avacopan for people with ANCA-associated vasculitis, subject to Special Authority criteria | High Priority |
| 13.5 | Avacopan for ANCA-associated vasculitis in a subset who are at the highest risk of adverse outcomes from high-dose steroid use, subject to Special Authority criteria | High Priority |
| 14.3 | Inclisiran for people with heterozygous familial hypercholesterolemia, subject to Special Authority criteria | High Priority |
| 15.3 | Pembrolizumab (Keytruda) for the first-line treatment of people with unresectable advanced malignant pleural mesothelioma, subject to Special Authority criteria | Decline |
| 15.4 | Pembrolizumab (Keytruda) for the first-line treatment of people with unresectable advanced non-epithelioid subtypes of malignant pleural mesothelioma, subject to Special Authority criteria | Medium Priority |

## 4. Record of PTAC meeting held 15 May & 16 May 2025

4.1. The Committee reviewed the record of the PTAC meeting held on 15 May & 16 May 2025

4.2. The Committee accepted the record.

## 5. Action Points

5.1. There are no current action points.

## 6. General Business

6.1. The Committee acknowledged the valuable and impactful contribution of Dr Scott Springford Metcalfe over his 30 years working at Pharmac. Members, past and present, have appreciated his championing of the principles and values of public health both within all advisory committees, but particularly PTAC. His passion to equitably achieve the best health outcomes for New Zealanders is a wonderful legacy.

## 7. Pharmac Update

7.1. The Committee noted the Pharmac Update.

7.2. The Committee acknowledged the introduction of new Pharmac kaimahi and ongoing leadership and strategic changes, including the upcoming commencement of the new Chief Executive in mid-September and the recent release of the 2025/2026 Letter of Expectations.

7.3. The Committee discussed the 5-year organisation reset programme and acknowledged that more information can be found on the Pharmac Website.

7.4. The Committee noted the continuation of the Medical Device Review, the societal perspectives workstream, and updates to the Rare Disorders Policy, which now aligns with the Aotearoa New Zealand Rare Disorders Strategy.

7.5. The Committee discussed the following updates to the record processes:

7.5.1. 30-day provisional recommendation trial update.

7.5.2. The Committee endorsed the removal of second committee reviews, with targeted reviews to be used as required, and supported the use of direct engagement with Discussion Leads to resolve outstanding issues.

7.6. The Committee acknowledged that the Close Out Project has transitioned into business as usual.

7.7. The Committee noted the information on options for managing items that have been on the OFI for an extended period of time.

## 8. Specialist Advisory Committee Record

### March 2025 Reproductive and Sexual Health Specialist Advisory Committee

8.1. PTAC reviewed the records of the Reproductive and Sexual Health Specialist Advisory Committee meeting held on the 13 March 2025.

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

### April 2025 Immunisation Specialist Advisory Committee

8.3. PTAC reviewed the records of the Immunisation Specialist Advisory Committee meeting held on 10 April 2025.

8.4. PTAC noted the record including the Advisory Committee's recommendations.

### March 2025 Interim Medical Device Advisory Group

8.5. PTAC reviewed the record of the first Interim Medical Devices Advisory Group meeting held in March of 2025.

## 9. Matters Arising: BIA assumptions for migraine proposals on the OFI

## Discussion

9.1. The Committee noted that Pharmac has received applications for the listing of Calcitonin Gene Receptor Peptide (CGRP) inhibitors - atogepant, erenumab, galcanezumab, and fremanezumab - for prophylaxis treatment of episodic migraine (EM) and chronic migraine (CM). The Committee noted that Pharmac was seeking advice from the Committee on several key uncertainties in the economic modelling, including the size of the eligible population and estimated uptake of treatment; duration of treatment with CGRP inhibitors; and the duration of disease for people with treatment-refractory migraine.

9.2. The Committee noted that erenumab for CM was considered by PTAC in August 2021 and August 2022, and that atogepant, erenumab, and galcanezumab for CM and EM were considered at the Neurological Specialist Advisory Committee (SAC) meeting in September 2023, and recommended for funding with a high priority. The Committee noted that an application for the listing of fremanezumab for CM and EM was being considered by PTAC at this meeting.

9.3. The Committee noted that a key uncertainty in the budget-impact analysis (BIA) is the number of people who may receive CGRP inhibitors for migraine, should these be funded. The Committee noted that advice was being sought on the prevalence of chronic and episodic migraine, how many of these people may be eligible for CGRP inhibitors, the likely uptake of treatment, and the applicability of the number of people receiving treatment in Australia as a proxy for New Zealand patient numbers.

9.4. Regarding prevalence of migraine more generally, the Committee considered that the prevalence of migraine in New Zealand is likely to be approximately 16%, based on the Global Burden of Disease study (GBD 2016 Headache Collaborators. Lancet Neurol. 2018;17(11):954-976). It was noted that this is similar to the reported prevalence in England of 14.3% (Steiner et al. Cephalalgia. 2003;23:519-527) and prevalence in the United States of America of 11.7-14.7% (Cohen et al. Headache. 2024;64(5):516-532). The Committee considered that given there was limited good quality New Zealand-specific evidence on the incidence and prevalence of migraine, it was appropriate to use estimated prevalence of migraine from the Global Burden of Disease report.

9.5. The Committee discussed what proportion of migraines are likely to be chronic. The Committee noted a systematic review on the prevalence and burden of migraine in the United States (Cohen et al. Headache. 2024;64(5):516-532) reported that 11.7% of all migraines were chronic, which would equate to 1.9% of the New Zealand population. The

Committee also noted a 2010 systematic review on the global prevalence of migraine (Natoli et al. Cephalalgia. 2010;30:599-609) reported a prevalence of CM in different countries of 1.4% to 2.2% (mid-point 1.8%). The Committee considered that the prevalence of chronic migraine in New Zealand is likely to be approximately 1.9% based on these publications.

9.6. The Committee considered data to inform the likely number of people with CM who have used at least three preventative treatments, as required in the CGRP inhibitor special authority criteria. The Committee noted a web-based self-referred questionnaire (Sanderson et al., J Neurol Neurosurg Psychiatry. 2013;84(12):1309–1317) of people over 18 years of aged with migraine. It reported that 28% of Australian people with chronic migraine had used at least three preventative treatments and 34% of people in the UK. The Committee noted that the study involved small patient numbers (600 people with CM and 600 people with EM), but considered it was the best data available at the time. The Committee considered that it was reasonable to assume 28% of people with CM have used at least three preventative treatments. The Committee considered this to be a better source than the US longitudinal web-based study (Lipton et al. Headache. 2022;62:122-40) which only reported the number actively using preventers.

9.7. The Committee discussed the likely uptake of CGRP inhibitor treatments, and considered that this was a highly uncertain parameter given the potentially substantial eligible population. The Committee noted uptake of treatment from a US retrospective cohort study (Khodavirdi AC, et al., Front. Neurol, 2024; 15:1433423) that found 29% of people with CM were on CGRP inhibitors and 80% were on traditional migraine prevention treatments. The Committee noted that the study was undertaken in 2019 and that treatment patterns may have subsequently changed. The Committee also considered that US healthcare system is very different to New Zealand, which is likely to affect uptake. The Committee considered the applicability of this study was unclear. The Committee therefore considered that uptake cannot be reliably estimated from epidemiological data with any certainty.

9.8. The Committee considered the number of people with EM who would likely access CGRP inhibitor treatment. The Committee noted that 2024 systematic review of migraine prevalence in the United States (Cohen et al. Headache. 2024;64(5):516-532) reported that 88.3% of all migraine in the United States were EM, and 30% of all EM people had at least four migraine days per month. The Committee noted a 2013 publication of health resource utilisation data collected via a web-based questionnaire (Sanderson et al. J Neurol Neurosurg Psychiatry. 2013; 84(12):1309–1317), which found that 12% of Australian people with EM had used at least three preventative treatments. The Committee considered it is reasonable to assume that approximately 50% of people who have used at least three preventative treatments would have at least four migraine days per month. The Committee considered studies on the likely uptake of CGRP inhibitors in people who meet the criteria for treatment. The Committee noted a retrospective cohort study of treatment patterns in patients with migraine eligible for CGRP inhibitor treatment (Khodavirdi AC, et al., Front. Neurol, 2024; 15:1433423) reported that 6.9% of the highest tertile US EM patients were on CGRP inhibitors. The Committee noted the following cohort studies and claims analyses provided data to inform rates of persistence on treatment:

- Ashina et al. Eur J Neurol 2021;28:1716-25
- Bjork et al. European Journal of Neurology, 2023; 31(1):e16062
- De Dios et al. Headache 2025;65:24-34
- Diaz Insa Pain Ther 2024;13:557-76
- Ferrari et al. J Neurol Neurosurg Psychiatry 2022;93:254-62
- Gladstone et al. Headache. 2021;62(1):78–88
- Hyeraci et al. Headache 2023;63:1391-402
- Kang M et al. J Clin Med. 2025;14(3):734
- Ray et al. BMJ Neurol Open 2024;6(1): e000547
- Swart et al., J Manag Care Spec Pharm. 2025;31(3):236–244
- Varnado et al. Patient Prefer Adherence 2022;16:821–839OJ

9.12. The Committee considered that there was noteworthy variation in these international estimates of the number of people who were likely to remain on treatment at 12 months. The Committee estimated that the available Australian market data indicated persistence on treatments for chronic migraine of 80% at 12 months and 67% at 18 months, based on the number of prevalent patients reported in the Australian patient numbers to be on treatment in Year 2 having started in Year 1 (PBS. Galcanezumab and Fremanezumab review. 2024). These estimates were noted to be limited by some people starting treatment part-way through the first year and being counted as continuing treatment in the second year regardless of whether treatment lasted more than 12 months. The Committee considered that overall, the international evidence indicates that persistence rates for those with chronic migraine were between 45-60% at 12 months, and closer to 60-70% for those with episodic migraine.

9.13. The Committee noted that the rates of persistence in cohort studies appeared higher than response rates in clinical trials, but considered that the treatment continuation rates in observational cohorts were likely to be a more reliable source for estimating rates of treatment continuation in a New Zealand setting. The Committee considered there were multiple reasons for the difference between response rates in trials and continuation rates in cohorts, including recall bias in clinical cohorts, and people in real world cohorts knowing they are on an active and effective treatment.

9.14. The Committee considered that while there may be some differences in effectiveness across migraine treatments, that there was little strong difference to inform the extent to which rates of persistence differed for each CGRP inhibitor and therefore that it was reasonable to assume persistence rates were similar across these treatments. However, the Committee considered there to be a substantial degree of variation and uncertainty across publications, and also uncertainty in the estimates derived from the Australian data, given the methods used to derive time on treatment were not particularly clear.

9.15. The Committee noted that there was limited evidence on the discontinuation rates of CGRP-inhibitors beyond 12-24 months. The Committee noted that Pharmac staff had estimated annual discontinuation rates on erenumab of 14% from month 12 to 24, and 5% in subsequent years, based on the erenumab long-term extension data. The Committee considered that this appeared to be a reasonable estimate for long-term discontinuation. The Committee considered that while there was no evidence available to inform whether discontinuation rates long-term would differ for each CGRP-inhibitor, that it was probably reasonable to assume that all CGRP inhibitors had a similar long-term rate of discontinuation based on the erenumab evidence.

9.16. The Committee noted an alternative method to estimate patient numbers is based on the number receiving treatments in similar markets to New Zealand, such as Australia. The Committee noted that Australia funds galcanezumab, eptinezumab, and fremanezumab for chronic migraine, and that access to fremanezumab was widened in November 2023 to include episodic migraine. The Committee considered the main difference between the Australian and New Zealand contexts appeared to be that CGRP inhibitors could only be prescribed by neurologists in Australia. However, the Committee considered that this was unlikely to impact the number of people using CGRP inhibitors because access to neurologists was easier in Australia compared to New Zealand, and so this may not constitute a major barrier in Australia. The Committee also considered that uptake may be

slightly higher in New Zealand due to lower use of botulinum toxin for CM, and therefore fewer effective treatments for this patient group. However, overall the Committee considered that using the Australian patient numbers as a proxy for the size of the New Zealand patient population was likely to be more appropriate than using an epidemiological approach, given the varied estimates of inputs to an epidemiological approach across the literature, in particular in the extent of uptake and persistence on treatment.

9.17. The Committee noted that, based on script data from 2021-2024, the median number of days on galcanezumab in Australia was 363 days, and median days on fremanezumab was 661 days. The Committee noted that, based on the observed number of people in Australia on fremanezumab or galcanezumab for CM in year 1 and 2 (and scaling up by 10% to allow for eptizenumab), there would be approximately 3,400 people in New Zealand on treatment in year one and 4,600 in year 2. The Committee noted that there was only good quality evidence on patient numbers out to two years, and that after this point, the curves would need to be extrapolated, which was acknowledged to be a key point of uncertainty.

9.18. The Committee noted that the Australian patient numbers primarily reflect those with chronic migraine, and that there was little evidence on the number of people receiving CGRP inhibitors for episodic migraine. The Committee considered that it was therefore very uncertain how much larger the patient population would be if both episodic and chronic migraine treatments were available, compared with if treatment was only available for chronic migraine. The Committee said a best guess is that the population would be roughly double if treatment was also available for the episodic migraine indication, given that the available evidence appeared to suggest the episodic migraine population may be 60-70% larger than that for chronic migraine, but the rate of non-response to three or more preventers was likely to be lower, and therefore the need for, and uptake of, CGRP inhibitors may be slightly lower for those with episodic migraine.

9.19. The Committee considered the duration of illness for people with treatment-refractory migraine. The Committee noted that the prevalence of migraine peaks at 40-50 years of age and declines thereafter, as reported in the Global Burden of Disease publication (GBD 2016 Headache Collaborators. Lancet Neurol. 2018;17(11):954-976). The Committee considered that based on their clinical experience, severe episodic and chronic migraine is generally uncommon after the age of 60 years. The Committee considered it was uncertain how many people would see their migraine resolve as they aged, and that any estimates were based on the observed relationship between age and prevalence, rather than longitudinal evidence. The Committee considered that a best guess is that approximately 50% of people who experience regular migraines would find that these cease between age 40 and 75 years, and possibly 80% of people using CGRP inhibitors at younger ages would move from experiencing severe migraines to mild migraines between the ages of 40 and 75 years, and therefore no longer require CGRP inhibitors. However, this was noted to be highly uncertain.

9.20. The Committee discussed the extent to which, if one CGRP inhibitor were funded, there would remain an unmet need for a second CGRP inhibitor. The Committee considered that the evidence indicates that there would likely be a group of people who would either experience a non-response to the first CGRP inhibitor or would lose benefit from a CGRP inhibitor over time. The Committee estimated that possibly 50% of people trialling a first-line CGRP inhibitor would require a second-line CGRP inhibitor but considered that this was highly uncertain and may need to be investigated further. The Committee also considered that while the evidence was generally of relatively low quality, that the available non-randomised evidence appeared to indicate that CGRP inhibitors offer a benefit in a second-line setting. The Committee discussed that though it appeared that response rates to a second CGRP inhibitor appeared lower than the first, as reported by de Dios 2025 (De Dios et al. Headache 2025;65: 24-34), the evidence of this was of relatively low quality.

## 10. Fremanezumab for chronic and episodic migraine

### Application

10.1. The Committee reviewed the application for Fremanezumab in the treatment of chronic migraine and episodic migraine.

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 fremanezumab be funded for the treatment of chronic migraine with a **high priority**, subject to the following Special Authority criteria:

> **Initial application** – (Chronic Migraine)
> Applications from a relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1. Individual has chronic migraine defined as experiencing at least 15 headache days per month (with at least 8 days having headache with migraine features), for at least 3 months; and
> 2. Individual has experienced an inadequate response, intolerance or a contraindication to at least three funded prophylactic migraine medications.
>
> **Renewal** - From any relevant practitioner. Approvals valid for 6 months for those who experience a reduction in monthly migraine days of at least 30% compared with baseline.

10.4. The Committee **recommended** that fremanezumab be funded for the treatment of episodic migraine with a **high priority**, subject to the following Special Authority criteria:

> **Initial application** – (Episodic Migraine)
> Applications from a relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1. Individual has episodic migraine defined as experiencing at least 4 migraine days per month for at least 3 months; and
> 2. Individual has experienced an inadequate response, intolerance or a contraindication to at least three funded prophylactic migraine medications
>
> **Renewal** - From any relevant practitioner. Approvals valid for 6 months for those who experience a reduction in monthly migraine days of at least 50% compared with baseline.

10.5. In making these recommendations the Committee considered:

10.5.1. The high and unmet health need for individuals with chronic or episodic migraine, their whānau, and society.

10.5.2. The Committee considered fremanezumab to offer a meaningful health benefit, with available evidence indicating a comparable reduction in the overall burden of migraine to that observed with other CGRP-targeted treatments under consideration by Pharmac (atogepant, erenumab, and galcanezumab).

10.5.3. That funding at least one CGRP-targeted medicine would result in significant benefits to people with migraine, the health system and wider society, but funding multiple agents would be preferred.

10.5.4. The limited efficacy and associated adverse risk profile associated with currently funded medicines used in the treatment of migraine.

### Discussion

*Māori impact*

10.6. The Committee discussed the impact of funding fremanezumab on Māori health outcomes. Members noted that migraine is not among the five Māori health areas of focus | Hauora Arotahi.

10.7. The Committee noted that migraine prevalence among Māori is reported to be similar to the general population. However, members considered that access to primary care and specialist services were likely reduced for Māori. The Committee was made aware that Māori experience chronic pain at a higher rate than other ethnicities and exhibit a lower rate of accessing chronic pain services (Devan et al. N Z Med J. 2021;134:19-29).

*Populations with high health needs*

10.8. The Committee discussed the health needs among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee noted that these populations were not represented in the pivotal clinical trial, and no population-specific evidence was available to inform outcomes for these groups.

*Background*

10.9. While acknowledging that additional diagnostic features apply, the Committee noted the following migraine categorization for the purposes of the discussion:

10.10.1. Episodic Migraine (EM): At least 4 migraine days per month, for at least three months, and does not meet criteria for chronic migraine.

10.10.2. Chronic Migraine (CM): At least 15 or more headache days per month (with at least eight days having headache with migraine features).

10.10. The Committee noted that fremanezumab is the latest of four calcitonin gene-related peptide (CGRP)-targeted medicines that Pharmac is considering for CM and EM.

10.11. The Committee noted that Pharmac last received clinical advice on CGRP-targeted medicines (atogepant, erenumab, and galcanezumab) from the Neurological Advisory Committee in September 2023. The Committee noted that the Neurological Advisory Committee had recommended funding with a high priority for the reviewed CGRP-targeted medicines for both CM and EM. Despite differences in how trial outcomes were reported, the reviewed agents were considered to offer similar reductions in monthly headache days. (link to September 2023 Record of the Neurological Advisory Committee Meeting).

10.12. The Committee noted the letters of support from the Migraine Foundation Aotearoa New Zealand and the Australia and New Zealand Headache Society that were included in the supplier application. Members noted having reviewed the previous submission from the Migraine Foundation Aotearoa New Zealand which was considered by the Neurological Advisory Committee at its September 2023 meeting.

*Health need*

10.13. The Committee considered the health needs of those living with CM or EM to be comprehensively documented in the Neurological Advisory Committee meeting record on review of CGRP antagonists (link to Sep 2023 record). Specifically, members agreed and reiterated that:

10.13.1. People living with EM or CM have a high and unmet health needs in Aotearoa New Zealand (NZ), in part due to the lack of funded migraine-specific treatments.

10.13.2. Compared to people with EM, those with CM experience a higher health need.

10.13.3. There is limited access to neurology or migraine specialist care within the publicly funded health system.

10.13.4. Women experience higher rates of migraine and are more restricted in the treatments than can be used, particularly for those of childbearing potential.

10.14. The Committee discussed the substantial impacts of EM and CM on quality of life, including schooling, employment, daily activities, and whānau life, and that some

individuals require acute care during severe episodes. The Committee considered that measures of disability, functional impairment, and quality of life provide essential context beyond headache-day counts, offering a more complete picture of the burden of migraine on individuals.

*Health benefit*

10.15. The Committee noted that CGRP-targeted medicines act on the different parts of the trigeminal system. Some monoclonal antibodies target the CGRP ligand (fremanezumab, and galcanezumab). Erenumab, in contrast, is a fully human monoclonal antibody that targets the canonical CGRP receptor. Members noted that atogepant is a small-molecule CGRP inhibitor.

10.16. The Focus Study was identified as key evidence (Ferrari et al. Lancet. 2019;394:1030-40). FOCUS was a randomised, placebo-controlled, double-blind, multi-national Phase III study which recruited participants with CM or EM who had a failure of two to four classes of migraine preventive medications in the past 10 years. The Committee noted that 50% of the study population had received three or more prior treatments and acknowledged the sub-population analysis from this group provided in the supplier application. Participants were assigned to receive fremanezumab monthly (n=283), fremanezumab quarterly (n=276), or placebo (PBO, n=279) for a 12-week controlled study period.

10.16.1. The Committee noted at the end of the 12 week controlled study period, participants with CM who received fremanezumab experienced a greater mean reduction in monthly migraine days from baseline compared to those receiving placebo (monthly fremanezumab vs placebo: −3.8 [95CI: −4.8 to −2.8, p<0.0001]; quarterly fremanezumab vs placebo: −3.2 [95CI: −4.2 to −2.2, p<0.0001]). This reduction in monthly migraine days was also observed in those with EM (monthly fremanezumab vs placebo vs PBO: −3.1 [95CI: −4.0 to −2.3], p<0.0001; quarterly fremanezumab vs placebo: −3.1 [95CI: −3.9 to −2.2], p<0.0001]).

10.16.2. The Committee considered that the safety profile associated with receiving fremanezumab was similar to that associated with receiving placebo. The most common adverse events across all study arms were injection-site erythema, injection-site induration, and nasopharyngitis. The Committee considered that the injection-site reactions described are typical for subcutaneous administration.

10.16.3. The Committee noted that less than 1% of patients receiving fremanezumab had an adverse event leading to discontinuation.

10.16.4. The Committee noted improvements in patient-reported outcomes in those receiving fremanezumab compared to those receiving placebo, including disability scores (HIT-6 and MIDAS), quality of life (MSQOL), and overall health status (EQ-5D). Members considered that these scoring systems have established minimally clinically important differences (MCIDs), which may differ from statistically significant changes that are not necessarily clinically meaningful. Specifically, the Committee noted the relative change in baseline MIDAS score compared to placebo, which was –12.7 for quarterly fremanezumab compared to placebo ($p < 0.0001$), which was considered to represent a meaningful clinical difference (Speck et al. Headache 2021;61:511-26). Overall, the Committee considered fremanezumab to offer significant benefits in terms of quality of life, disability reduction, and improvements in work productivity and functional impairment (Ferrari et al. Lancet. 2019;Supplemental Table 9 and Spierings et al. Headache. 2021;61:1376-86).

10.16.5. The Committee considered that both fremanezumab arms in FOCUS (monthly and quarterly dosing) demonstrated comparable health benefits.

10.16.6. The Committee discussed the quality of evidence provided by the FOCUS study. Members noted that the trial and its associated publications were sponsored by the supplier of fremanezumab. Overall, members considered the evidence from this trial to be of acceptable quality, and comparable to that of other studies involving CGRP-targeted medicines.

10.16.7. The Committee discussed the applicability and relevance of the evidence provided by the FOCUS study, noting that participants were recruited across Europe (mostly Czech Republic) and the USA. The Committee acknowledged that the NZ treatment landscape—including the availability of migraine medicines and access to care (e.g. general practitioners, specialists, treatment monitoring)—differs from that of the study population. Overall, members considered that it reasonable to expect the study findings to be generalisable to the New Zealand context.

10.17. The Committee noted real-world studies which reported:

10.17.1. Fremanezumab maintained its therapeutic benefit for the duration of the 12-month treatment period that was assessed (Ashina et al. Cephalalgia. 2023;43).

10.17.2. People receiving fremanezumab had fewer emergency room and outpatient visits compared to the period when they were not receiving fremanezumab (McAllister et al. J. Headache Pain. 2021;22:156).

10.17.3. People who discontinued erenumab due to adverse events (predominately constipation) appeared to be able to tolerate fremanezumab (Amin et al. J Headache Pain. 2025;26:152).

10.18. The Committee considered that the real-world evidence was broadly consistent with the findings of the FOCUS trial, however it noted that the observed 50% responder rates were higher than those reported in FOCUS. Additionally, the Committee noted that hepatotoxicity, constipation, and hypertension that were anticipated to occur with CGRP-targeted medicines were not observed in the real-world evidence.

10.19. The Committee considered that longer-term safety data from beyond 12 months would be valuable to comprehensively understand the long-term risks associated with persistence on fremanezumab.

10.20. The Committee noted the indirect-treatment comparison (ITC) contracted by the supplier, which was conducted by the Statistical Consulting Centre at the University of Melbourne. The analysis used separate placebo-controlled trials to compare the safety and efficacy of fremanezumab to atogepant, erenumab, and galcanezumab.

10.20.1. The Committee acknowledged the Supplier's use of this analysis to suggest fremanezumab is at least non-inferior to atogepant, erenumab, and galcanezumab in terms of efficacy and safety. The Committee considered that the lack head-to-head controlled trials as a limitation for assessing their comparative treatment effects. The Committee noted that trial-to-trial differences – variability in eligibility criteria (such as the number of prior prophylactic therapies), headache/migraine definitions, endpoints, dose, assessment periods, duration of treatment, route of administration for placebo responses – impede high-confidence evidence-based comparisons.

10.20.2. The Committee considered several independently conducted independent treatment comparisons which investigated the comparative efficacy and safety of CGRP-targeted medicines, including:

- Ailani et al. Cephalalgia. 2024;44:11
- Haghdoost et al. Cephalalgia. 2023;43
- Misty et al. Health Technol Asess. 2024;28:1-329
- Haridas et al. Clin Psychopharmacol Neurosci. 2024;22:23-32
- Oliveria et al. J Headache Pain. 2024;25:51

10.20.3. The Committee noted that several statistically significant findings were reported in these independent analyses; however, members questioned the relevance and validity of these differences to real-world clinical practice. As with the Melbourne University ITC, the comparisons were considered to be undermined by inter-trial variability. The Committee discussed that no single CGRP monoclonal antibody (mAb) has been clearly demonstrated to have superior efficacy. Overall, the Committee considered that the available evidence indicates fremanezumab has comparable efficacy to atogepant, erenumab, and galcanezumab. The Committee

reviewed the safety profiles between anti-CGRP mAbs and oral gepants and considered that their tolerability appeared to be broadly similar. The Committee considered that differences in the suitability of these agents are likely to determine their practical use and preference in real-world settings.

10.22. The Committee discussed atogepant as a small-molecule CGRP antagonist capable of crossing the blood–brain barrier, which was considered to be associated with differences in its safety profile compared to CGRP-targeted monoclonal antibodies.

10.23. The Committee was made aware of increasing reports that people may switch between CGRP-targeted medicines or seek add-on use (for example, with botulinum toxin or one monoclonal antibody combined with one oral agent; Versijpt et al. Lancet. 2025;405:1014-26). The Committee discussed the utility of medicine holidays, combination therapy with CGRP-targeted medicines, and switching between agents as emerging areas of research. The Committee considered that if more than one agent were to be funded, there would be a desire to switch between treatments or combine agents (e.g. an oral agent and a monoclonal antibody). The Committee considered that further work is needed to generate evidence-based guidance on discontinuation strategies and switching between or combining medicines targeting the CGRP pathway.

10.24. The Committee noted the European Headache Federation and the American Headache Society position on CGRP- targeted medicines as first-line options but considered this approach may currently be cost prohibitive in NZ.

10.25. The Committee noted obesity associated resistance to be an emerging research area and considered there to be uncertainty about effective benefits from CGRP-targeted treatment at current dose and administration regimens.

*Suitability*

10.26. The Committee noted that fremanezumab is administered subcutaneously using a pre-filled syringe and can be self-administered at home after initial training provided by a health care professional, with a small proportion of people requiring ongoing assistance.

10.27. The Committee noted two fremanezumab dosing schedules: monthly dosing and three-monthly dosing (administered as three injections at one time). The Committee considered that people are likely to prefer three-monthly administration to monthly dosing, and reiterated the available evidence demonstrated that using either regimen is sufficient to achieve the treatment effect.

10.28. The Committee noted that the factors related to suitability were different between the four CGRP-targeted medicines that Pharmac is considering. Members acknowledged that individual preference would vary between the subcutaneously administered mAbs and atogepant, which is taken daily as an oral tablet. The Committee considered that people with migraine would value having the option to choose between an oral or subcutaneous CGRP-targeted medicine.

*Cost and savings*

10.29. The Committee considered that conducting a competitive procurement process for a single agent to be possible but it may not be the preferred option. The Committee expressed a preference for more than one funded option (ideally at least one monoclonal antibody and one oral gepant), while noting that funding a single medicine would still be valuable if required by budget constraints.

10.30. The Committee noted there is a resource barrier to implementing subcutaneous agents such as fremanezumab, because of the resource demand on primary care associated with administration training and medicine access.

*Funding criteria*

10.31. The Committee noted the clinical relevance of outcomes relating to quality of life, disability, and functional impairment for medication renewal decisions. Members considered that only a small proportion of people were likely to experience a 30-50% reduction in monthly migraine days and therefore meet the proposed renewal criteria.

However, the Committee considered that a much larger proportion would be expected to meaningfully benefit from treatment with a CGRP-targeted medicine, and that rates of continuation on treatment in cohorts outside of NZ appear to be higher than the number of people experiencing a 30-50% reduction in monthly migraine days.

10.32. The Committee also noted that improvements in migraine severity, even without a reduction in frequency, represents a meaningful benefit for people with migraine. The Committee considered that in practice, symptoms were likely to fluctuate over time, and even if patients completed a migraine diary, the number of people reporting a 30-50% improvement would be higher than in the key trial evidence due to imperfect recall and the potential for migraine days to be subjectively recorded. The Committee considered that a stricter set of criteria may therefore be difficult to effectively implement. The Committee suggested Pharmac should consider whether strict renewal criteria should be used, or if renewal should be left to prescriber discretion to decide if a person continues to benefit from treatment. The Committee suggested that Pharmac could consider outcomes related to hospital visits, return to workforce, depression, acute headache medication use, severity of headache, caregiver impact, and family time/relationships.

10.33. The Committee considered the initial approval duration of three months to be appropriate.

*Summary for assessment*

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

| | | |
|---|---|---|
| **P**opulation | Episodic Migraine<br><br>People with at least 4 migraine days per month for at least 3 months, and who do not meet the criteria for chronic migraine, and who have experienced an inadequate response, intolerance or a contraindication to at least three funded prophylactic migraine medications. | Chronic Migraine<br><br>People with at least 15 headache days per month (with at least 8 days having headache with migraine features) for at least 3 months, and who have experienced an inadequate response, intolerance or a contraindication to at least three funded prophylactic migraine medications. |
| **I**ntervention | Fremanezumab (AJOVY) – subcutaneous, prefilled syringe (225 mg/1.5 mL), once monthly, or 3 syringes quarterly. | |
| **C**omparator(s) (NZ context) | Current 4th line treatment with recommended available prophylactic agents.<br>• propranolol or other beta-blocker (eg metoprolol or nadolol)<br>• amitriptyline<br>• topiramate<br>• pizotifen<br>• sodium valproate (not for those of childbearing potential) | |
| **O**utcome(s) | **Primary outcomes**<br><br>Reduction in the mean number of headache/migraine days per month (>50% reduction)<br><br>Reduced days per month requiring acute migraine medication.<br><br>**Health-related quality of life outcomes**<br><br>Improvements in MSQOL, MIDAS, and EQ-5D. | **Primary outcomes**<br><br>Reduction in the mean number of headache/migraine days per month (>30% reduction)<br><br>Reduced days per month requiring acute migraine medication.<br><br>**Health-related quality of life outcomes**<br><br>Improvements in MSQOL, MIDAS, and EQ-5D. |
| **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | | |

## 11. Tirzepatide (Mounjaro) for the treatment of insufficiently controlled type 2 diabetes mellitus

### Application

11.1. The Committee reviewed the application for tirzepatide in the treatment of insufficiently controlled type 2 diabetes mellitus, as an adjunct to diet and exercise.

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 tirzepatide for type 2 diabetes mellitus be listed with a **medium priority**, subject to the following Special Authority criteria:

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

1. Patient has type 2 diabetes; and
2. Target HbA1c (of 53 mmol/mol or less) has not been achieved despite the regular use of ALL of the following funded blood glucose lowering agents for a period of least 6 months, where clinically appropriate: empagliflozin, metformin, and vildagliptin; and
3. Any of the following:
   - 3.1. Patient has pre-existing cardiovascular disease or risk equivalent (see note a)*; or
   - 3.2. Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator*; or
   - 3.3. Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult*; or
   - 3.4. Patient has diabetic kidney disease (see note b)*.

Notes: * Criteria intended to describe patients at high risk of cardiovascular or renal complications of diabetes.

1. Pre-existing cardiovascular disease or risk equivalent defined as: prior cardiovascular disease event (i.e. angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack, ischaemic stroke, peripheral vascular disease), congestive heart failure or familial hypercholesterolaemia.
2. Diabetic kidney disease defined as: persistent albuminuria (albumin:creatinine ratio greater than or equal to 3 mg/mmol, in at least two out of three samples over a 3-6 month period) and/or eGFR less than 60 mL/min/1.73m$^2$ in the presence of diabetes, without alternative cause identified.
3. Funded GLP-1a treatment is not to be given in combination with [empagliflozin / empagliflozin with metformin hydrochloride] unless receiving (empagliflozin or empagliflozin in combination with metformin hydrochloride] for the treatment of heart failure.

11.5. In making this recommendation, the Committee considered:

- 11.5.1. The high health need of individuals with insufficiently controlled T2DM, with a substantial proportion of patients not achieving target HbA1c levels.
- 11.5.2. The unmet treatment need for individuals with sub-optimal glycaemic control despite current therapies.
- 11.5.3. The disproportionately higher prevalence of T2DM among Māori and Pacific peoples, contributing to significant health inequities.
- 11.5.4. The therapeutic advantages of tirzepatide, including superior HbA1c reduction and weight loss compared to GLP-1 receptor agonists.

## Discussion

*Māori impact*

11.6. The Committee discussed the impact of funding tirzepatide for the treatment of insufficiently controlled T2DM on Māori health areas of focus | Hauora Arotahi and Māori health outcomes.

- 11.6.1. The Committee noted that the Diabetes and Cardiovascular Subcommittees have previously acknowledged the extensive evidence showing that Māori experience a higher disease burden of diabetes, resulting in disproportionately worse outcomes, and experience a higher rate of mortality attributable to T2D than the general population.

11.6.2. The Committee noted in 2023, an estimated 323,700 New Zealanders were living with diabetes according to Te Whatu Ora's Virtual Diabetes Register (VDR). This equates to an age-standardised prevalence rate of 44.3 per 1,000 within the overall population. The Committee noted prevalence rates were disproportionately higher in Māori (71.6 per 1,000).

*Populations with high health needs*

11.7. The Committee discussed the health need(s) related to diabetes among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs.

11.7.1. The Committee noted that according to Te Whatu Ora's Virtual Diabetes Register (VDR), prevalence rates were also disproportionately higher in Indian (103.4 per 1,000) and Pacific (125.5 per 1,000) ethnicities, as well as those who lived in the most deprived socioeconomic areas (74.3 per 1,000).

*Background*

11.8. The Committee noted that advice pertaining to anti-diabetic agents for the treatment of T2DM has been provided on multiple occasions. For further details and the current status of these recommendations, please refer to the Pharmac Application Tracker.

11.8.1. The Committee noted that anti-diabetic agents (DDP-4 inhibitors, SLGT-2 inhibitors, and GLP-1 receptor agonists) for the treatment of type 2 diabetes mellitus (T2DM) were previously considered by the Diabetes Subcommittee in March 2019 and the Cardiovascular Subcommittee in May 2019.

11.8.1.1. The Committee acknowledged that the Diabetes Subcommittee noted a high health need of those with T2DM in New Zealand and the disproportionate disease burden that occurs in Māori, Pacific and Southeast Asian populations.

*Health need*

11.9. The Committee noted that the health need of individuals with T2DM has been well established in previous clinical advice regarding the use of SLGT-2 inhibitors and other GLP-1 agonists for managing T2DM in individuals with cardio-renal risk factors.

11.10. The Committee noted data from the New Zealand Health Survey (2023/2024) indicating a prevalence rate of known diabetes among New Zealanders aged 15 years and over (excluding gestational diabetes) at 6.4%, equating to approximately 278,000 adults. The Committee noted that T2DM is the most common form of diabetes and accounts for 90–95% of all diagnoses.

11.11. The Committee noted that an estimated 40–60% of individuals with T2DM have sub-optimal achievement of HbA1c targets, indicating poor glycaemic control in a substantial proportion of patients.

*Health benefit*

11.12. The Committee noted that tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, based on an amino acid sequence with a C20 fatty diacid moiety enabling albumin binding, which prolongs the half-life.

11.13. The Committee noted the SURPASS-2 trial (Frías J, et al. N Engl J Med. 2021;385:503-515), a phase 3, randomised, open-label 40-week study comparing the efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist.

11.13.1. The Committee considered that SURPASS-2 was a well-designed study and demonstrated consistent efficacy and adverse event profiles across treatment arms. The Committee noted 1879 participants were randomly assigned to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg.

11.13.2. The Committee noted that tirzepatide achieved greater HbA1c reductions when compared to semaglutide, with a mean change of -2.30% at the 15 mg dose vs. -1.86 with semaglutide (difference -0.45, 95% CI -0.57 to -0.32; *P*<0.001).

11.13.3. The Committee noted that reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, -1.9 kg (tirzepatide 5 mg), -3.6 kg (tirzepatide 10 mg), and -5.5 kg (tirzepatide 15 mg); P<0.001 for all comparisons).

11.13.4. The Committee noted that serious adverse events occurred in 5.7% of participants receiving tirzepatide 15 mg and 2.8% of those receiving semaglutide. The Committee noted the overall incidence of adverse events was high in both groups, predominantly gastrointestinal in nature, including nausea, diarrhoea, vomiting, dyspepsia, and anorexia.

11.13.5. The Committee noted that treatment discontinuation due to adverse events occurred in 8.5% of patients receiving tirzepatide 15 mg, compared with 4.1% in the semaglutide group.

11.14. The Committee noted the SUSTAIN-7 trial (Pratley et al. Lancet Diabetes Endocrinol. 2018;6(4):275-286), a phase 3b, randomised, open-label 40-week study which compared semaglutide with dulaglutide in participants with inadequately controlled type 2 diabetes.

11.14.1. The Committee noted that semaglutide was superior to dulaglutide in reducing HbA1c, with an estimated treatment difference (ETD) of -0.40% (95% Ci -0.55 to -0.25) at lower doses and -0.41 (95% CI -0.57 to -0.25) at higher doses (p<0.0001 for both comparisons).

11.14.2. The Committee noted that semaglutide also led to greater weight loss than dulaglutide, with an ETD of -2.26kg (95% CI -3.02 to -1.51) at lower doses and -3.55 kg (95% CI -4.32 to -2.78) at higher doses (p<0.0001 for both).

11.14.3. The Committee noted that the adverse event profiles of semaglutide and dulaglutide were broadly similar, with gastrointestinal disorders being the most common in both groups. The Committee noted these were consistent with those observed in the tirzepatide versus semaglutide comparison.

11.15. The Committee noted that the treatment effects of dulaglutide 1.5 mg used in the economic evaluation were appropriately derived from an indirect comparison of the SURPASS-2 and SUSTAIN-7 trials, which were considered sufficiently similar in terms of glucose and weight management outcomes.

11.16. The Committee was made aware of a comparative systematic review and network meta-analysis evaluating the effectiveness of GLP-1 receptor agonists on glycaemic control body weight, and lipid profile in individuals with T2D. (Yao, et al. BMJ. 2024;384:e076410)

11.16.1. The Committee noted that tirzepatide demonstrated the greatest HbA1c reduction among all GLP-1RAs included in the analysis, with a mean difference of -2.10% (95%CI: -2.47 to -1.74) compared to placebo.

11.17. The Committee noted that the evidence supporting tirzepatide for glycaemic control, weight loss, and adverse events is of high quality, based on well-conducted randomised trials and network meta-analyses.

11.18. The Committee noted that the evidence supporting tirzepatide is generalisable and relevant to the New Zealand context, with study populations and treatment settings broadly comparable to those seen in New Zealand.

11.18.1. The Committee noted that trial populations excluded individuals with proliferative retinopathy, which may limit generalisability to this subgroup.

11.18.2. The Committee noted individuals with proliferative retinopathy were excluded from the key trial. Members considered that the diagnosis of eye disease would be required prior to treatment initiation, which may produce additional demand on ophthalmology services.

11.19. The Committee noted that traditional outcome measures in type 2 diabetes have relied heavily on surrogate markers such as HbA1c, based on long-term evidence from landmark trials including UKPDS (T2D) and DCCT (T1D). The Committee also noted emerging questions about the suitability of HbA1c as a surrogate endpoint in the context of modern treatment agents. Members considered newer therapies deliver broader clinical benefits beyond glycaemic control, prompting consideration of comparative outcomes and patient-reported measures such as health-related quality of life (HRQoL).

11.20. The Committee expressed a preference for real-world data to inform clinical outcome extrapolation within the modern treatment paradigm, rather than relying on long-term historical data, such as the UKPDS. The Committee noted that there is currently a lack of suitable real-world evidence

11.21. The Committee was made aware of preliminary results from the SURPASS-CVOT (press release dated 31 July 2025) trial indicating that tirzepatide was non-inferior to dulaglutide for major adverse cardiovascular events (MACE), with a reported hazard ratio of 0.92 (95% CI: 0.83 to 1.01). Unadjusted all-cause mortality was also lower in the tirzepatide group (HR 0.84; 95% CI: 0.75 to 0.94). The Committee acknowledged these are unpublished data, pending full publication and peer review.

11.22. The Committee noted that tirzepatide is likely to provide additional benefits compared with currently funded alternatives for this population, particularly in terms of improved glycaemic control and greater weight reduction.

11.23. The Committee discussed whether there may be a distinct subgroup who could derive additional benefit from tirzepatide beyond those currently eligible for GLP-1RA treatment. While evidence is limited, the Committee noted that individuals currently using dulaglutide but not achieving glycaemic targets may benefit from switching to tirzepatide, given its greater potency in lowering HbA1c and promoting weight loss.

*Suitability*

11.24. The Committee noted that tirzepatide is administered once weekly via subcutaneous injection, similar to dulaglutide, and requires gradual dose titration to mitigate gastrointestinal side effects.

11.25. The Committee considered tirzepatide offers advantages over insulin regimens in terms of ease of use, patient acceptability, and a very low risk of hypoglycaemia, which may enhance safety and tolerability.

11.26. The Committee noted that weight reduction is likely a key contributor to its overall clinical benefit in people with T2D.

*Cost and savings*

11.27. The Committee considered that interpreting the economic modelling was challenging due to its complexity, particularly where it relies on data from sources such as the UKPDS. The Committee acknowledged that, while the modelling implies substantial changes in mortality and MACE, these outcomes have not yet been clearly demonstrated in a single, consolidated study.

11.28. Committee members considered the potential benefits of improved diabetes control, as evidenced by reductions in HbA1c, in delaying or preventing the progression of diabetes-related chronic kidney disease. Such potential benefits might be considered in health economic modelling of tirzepatide.

11.28.1. Committee Members acknowledged the limitations of current data, particularly the discrepancy between historical assumptions regarding surrogate markers and outcomes from recent studies, and noted the uncertainty around whether health impacts are correlated solely to HbA1c or incorporated other measures. The Committee recognised the high uncertainty regarding the association between HbA1c and end-organ disease, particularly given the changes in treatment landscape between the landmark UKPDS and DCCT studies and the current paradigm.

11.28.2. The Committee noted that the results of the SURPASS-CVOT trial, when published, would provide additional certainty around the cardiovascular and renal benefits associated with tirzepatide therapy.

*Funding criteria*

11.29. The Committee considered the proposed Special Authority criteria were appropriate to target the population who would benefit the most.

*Summary for assessment*

11.30. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for tirzepatide if it were to be funded in New Zealand for insufficiently controlled type 2 diabetes. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | |
|---|---|
| **P**opulation | New Zealand patients aged 18 years and over with:<br>• type 2 diabetes; and<br>• Target HbA1c >53 mmol/mol despite use of alternative glucose lower agent for 3 months; and<br>• One of the following:<br>  ○ Patient has pre-existing CVD or risk equivalent<br>  ○ Patient has an absolute 5-year CVD risk of ≥15%<br>  ○ Patient has high lifetime CV risk due to being diagnosed with T2D at a young age<br>  ○ Patient has diabetic kidney disease |
| Intervention | Tirzepatide; 2.5 mg – 15 mg (weekly, subcutaneous injection) |
| **C**omparator(s) (NZ context) | Dulaglutide 1.5 mg (once a week, subcutaneous injection) |
| **O**utcome(s) | Improved glycaemic control, reduced cardiovascular risk factors such as blood pressure, cholesterol, and body weight.<br>Impact on long-term macrovascular and microvascular complications such as stroke, myocardial infarct, heart failure, renal failure, amputations, and associated morbidity and mortality associated with these complications. |

*Table definitions:*

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

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

**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

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

## 12. Biosimilar to biosimilar evidence review – rituximab and adalimumab

### Application

12.1. The Committee reviewed a request from Pharmac staff regarding potential future biosimilar to biosimilar changes of intravenous (IV) rituximab (ritux-ritux) and/or subcutaneous (SC) adalimumab (ada-ada) for their respective funded indications.

12.2. The Committee noted that advice was not specifically sought regarding consumer-facing implementation plans (eg timing, materials) at this time, and that these plans would require input from relevant Specialist Advisory Committee advisors and development as part of a procurement approach.

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

### Recommendation

12.4. The Committee **recommended** that it was clinically acceptable for Pharmac to progress a competitive procurement process for rituximab that could result in a different rituximab biosimilar being listed and being the only available rituximab product for all funded indications, if the cost saving is worthwhile and supply is secured.

12.5. In making this recommendation, the Committee:

12.5.1. considered that data for a change from one rituximab biosimilar to another rituximab biosimilar was very limited, being in a small number of individuals from case series and observational studies. However, the Committee considered that this supported a change between rituximab biosimilars and that there was no evidence to indicate changes in efficacy or adverse-event profiles as a result of the change

12.5.2. noted that the evidence included only haematological indications, however, considered that this conclusion could be reasonably applied to all currently funded indications for rituximab

12.5.3. noted the need for change-management and consumer-focused education and implementation strategies to support success.

12.6. The Committee **recommended** that it was clinically acceptable for Pharmac to progress a competitive procurement process for adalimumab that could result in a different adalimumab biosimilar being listed and being the only available adalimumab product for all funded indications, if the cost saving is worthwhile and supply is secured.

12.7. In making this recommendation for adalimumab, the Committee:

12.7.1. considered that systematic reviews and additional studies supported changing between biosimilars of adalimumab without loss of efficacy or increased adverse events.

12.7.2. noted the need for change-management and consumer-focused education and implementation strategies to support success; specifically, that clear communication and patient support would potentially minimise the nocebo effect and patient-reported experience deterioration.

12.7.3. considered that continuing to fund a citrate-free formulation would be preferable especially if funded for treatment for children and use in the community.

12.8. The Committee considered that Pharmac should seek advice from the Consumer Advisory Committee on messaging and consumer-facing materials ahead of any proposed change from biosimilar-to-biosimilar.

### Discussion

*Māori impact and populations with high health needs*

12.9. The Committee considered that no disproportionate impacts on people experiencing health inequities were identified in relation to biosimilar-to-biosimilar changes, and that there appeared to be no reason for this to worsen with such a change.

*Background*

12.10. The Committee noted that PTAC and other Advisory Committees had previously provided advice to Pharmac regarding appraisal of and considerations relating to implementation of biosimilars on several occasions. The Committee discussed some features of past experience transitioning from a funded reference biologic to a biosimilar (eg adalimumab).

12.11. Members discussed that from a regulatory perspective, biosimilars are compared to the reference biologic (not other biosimilars). The Committee noted that, similar to the variability between batches of a reference biological medicines, there may be small differences between biosimilars due to the molecules in these medicines being from living cells. The Committee considered that inter-individual variability may mean that some people sit outside comparative ranges despite overall equivalence at the population level.

12.12. The Committee noted that the term "cross switching" has been used internationally to describe biosimilar-to-biosimilar changes (switching) within a class (eg Mysler et al. Drugs. 2021;81:1859–79) and considered that the advice sought at this time related to a biosimilar non-medical cross-switch within the same class.

12.13. The Committee noted that there is a growing consensus of equivalence in safety and efficacy of many biosimilar monoclonal antibodies compared with the reference product, with regulators such as the US FDA expanding designations of interchangeability to include greater numbers of named biosimilar medicines. Specifically, the Committee noted the following views and statements:

- Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU, European Medicines Authority (EMA) and the Heads of Medicines Agencies (HMA). April 2023
- US Food and Drug Administration (US FDA) Drug Topics: Biosimilars - A review of scientific, regulatory and clinical considerations for health care providers, Brahme et al., US FDA. June 2023
- Considerations in Demonstrating Interchangeability with a Reference Product: Update, US FDA. June 2024
- Cohen et al. BioDrugs. 2024; 38: 331–39 (systematic review)

12.15. The Committee noted the international view that the clinical evidence base for interchangeability is of lower quality than that supporting the reference product, however, that the observational data suggest cross-switching can be clinically acceptable.

12.16. The Committee considered that international cross-switching practice is predominantly motivated by financial rather than clinical considerations, intended to generate cost savings. The Committee noted that a change from one biosimilar to another biosimilar may also involve expanding funding eligibility where financially appropriate, making it more available to more people.

*Rituximab*

12.17. The Committee noted the currently funded uses for rituximab (Riximyo and Mabthera) and the indications included in Named Patient Pharmaceutical Applications (NPPAs) for rituximab received and approved since 2024. The Committee noted the previous consideration of rituximab biosimilars by PTAC in February 2019 and the Cancer Treatments Subcommittee of PTAC (CaTSoP) in October 2019. The Committee noted that any future procurement process would reconsider the option to remove or significantly simplify any eligibility criteria for rituximab. The Committee noted that Pharmac has already received advice on removing or simplifying these criteria and further advice was not required at this time.

12.18. The Committee considered that equivalence of rituximab biosimilars to the reference product in treatment-naïve individuals has previously been established based on high-level evidence, and that the safety and effectiveness of changing from the reference rituximab to a biosimilar is supported by lower-level observational evidence. The Committee considered that the focus of this appraisal was the safety and effectiveness of changing between biosimilars, which would be expected to be based on lower-level observational evidence.

12.19. The Committee noted a single-centre prospective observational pilot study in Italy assessing the safety of switching between rituximab biosimilars (CT-P10 [Truxima] and GP2013 [Rixathon]) in haematological malignancies (Urru et al. Sci Rep. 2021 Mar 16;11:5956). The Committee noted that 26/83 (32%) were switched from one biosimilar to another in this study and had a median follow-up of 10.5 months (interquartile range: seven to 14 months). The Committee considered that this evidence did not identify new safety signals or loss of effectiveness.

12.20. The Committee noted a subsequent prospective multicentre observational study conducted in 13 onco-haematology units in Italy (N=505) which aimed to collect clinical information about any adverse drug reaction (ADR) related to the use of reference rituximab or biosimilars (Urru et al. Cancers (Basel). 2024;16:3419). The Committee noted that a subset (n=25) later switched from one biosimilar to another and that an apparent lower adverse-event rate in 'switchers' compared with 'non-switchers' was reported. The Committee considered that this apparent difference reflected selection bias because most 'switchers' moved back to the subcutaneous reference rituximab after initial intravenous dosing (a strategy commonly used in other jurisdictions for high-risk non-Hodgkin lymphoma once an initial IV infusion is tolerated to more easily allow more intensive rituximab therapy). The Committee consider that this patient selection and administration route change would be expected to alter observed adverse-event profiles.

12.21. The Committee was made aware of a patient cohort with rheumatoid arthritis in the UK (N=40) who switched to a biosimilar and noted that five individuals who switched developed serum sickness despite prior tolerance to the reference rituximab. Members considered the timing of these events, occurring months or years after the initial reference rituximab infusions, was unusual and not reported elsewhere (Nisar M. Rheum. 2019; 58 (Suppl_3):204).

12.22. The Committee considered that data for a change from a rituximab biosimilar to a rituximab biosimilar were very limited, being in a small number of individuals from case series and observational studies. However, the Committee considered that this supported a change between biosimilars and that there was no evidence to indicate changes in efficacy or adverse-event profiles as a result.

12.23. Overall, the Committee considered that a potential non-medical change from one biosimilar rituximab (Riximyo, current funded) to another biosimilar rituximab would be unlikely to jeopardize patient safety or efficacy outcomes. The Committee noted that the evidence included only haematological uses, however, considered that this conclusion could be reasonably applied to all currently funded uses for rituximab (as was the approach taken with the first change to biosimilar rituximab). The Committee supported Pharmac progressing a competitive procurement process that could potentially result in a non-medical change from biosimilar rituximab to another biosimilar rituximab.

12.24. The Committee noted that Pharmac | Te Pātaka Whaioranga's prior change from reference to biosimilar rituximab was reported by health professionals as seamless and rapid with minimal issues. The Committee considered that if changing is confined to intravenous formulations of rituximab biosimilars, impacts beyond the medicine cost would be minimal. The Committee considered that funding a subcutaneous formulation could be advantageous by potentially freeing some infusion centre capacity. However, members were made aware of anecdotal local experience that minimal chair-time differences might result once pre- and post-administration processes are included, tempering expectations of capacity gain.

*Adalimumab*

12.25. The Committee noted the currently funded uses for adalimumab (Amgevita and Humira); the indications included in Named Patient Pharmaceutical Applications (NPPAs) for rituximab received and approved since 2024; and previous consideration of adalimumab biosimilars by PTAC and other Advisory Committees.

12.26. The Committee noted evidence for switching between adalimumab biosimilars in the 2022 and 2024 systematic reviews reported by Cohen et al. which concludes that theoretical concerns of safety and efficacy impacts from multiple switches are not supported by the evidence (Cohen et al. BioDrugs. 2022;36:625-37; Cohen et al. BioDrugs. 2024; 38: 331–39).

12.27. The Committee noted an observational cohort study in a tertiary referral centre for inflammatory bowel disease (IBD) which included 35 individuals who switched from SB5 to ABP 501 ("double switch cohort") (Derikx et al. J Crohns Colitis. 2021;15:2011–21). The Committee noted that this appeared to suggest lower rates of adverse events (AEs) in those who switched to another biosimilar compared with those who did not, however, this was not statistically significantly different and the presence of citrate in one biosimilar may have been a factor as this is known to be associated with injection site pain AEs.

12.28. The Committee also noted the following:

- de Olivera Ascef et al. Sci Rep. 2023;13:13699
- Jensen et al. Arthritis & Rheum. 2024;76(Suppl 9):2046–9
- Parisi et al. Ann Rheum Dis. 2022;81(Suppl. 1):1295–6.
- Gall et al. Semin Arthritis Rheum. 2022 Dec:57:152119
- Lontai et al. Dig Liver Dis. 2022;54:1639-45
- Gall et al. Ann Rheum Dis. 2021;80:376.
- Ribaldone et al. J Clin Med. 2021;10:3387
- Scrivo et al. Clin Exp Rheumatol. 2023;41:613-9
- Vernero et al. J Clin Med. 2023;12):6839
- Fleischmann et al. Lancet Rheumatol.2023;5:e532-41
- Lebwohl et al. Adv Ther. 2025;42:1582-99
- Menter et al. Am J Clin Dermatol. 2022;23:719-28
- Gall et al. Semin Arthritis Rheum. 2022:57:152119

12.29. Overall, the Committee considered that there is substantially more evidence for biosimilar-to-biosimilar changes for adalimumab than for rituximab, with moderate to high level evidence systematic reviews and additional studies supporting changes both from reference adalimumab to biosimilar and between biosimilars without loss of efficacy or increased AEs. The Committee noted that the evidence covered a range of uses and considered that this conclusion applied to all currently funded uses for adalimumab.

12.30. The Committee noted that one possible future funding scenario is that lower prices achieved through procurement of an adalimumab biosimilar might enable widening of access to adalimumab for additional uses. The Committee considered that chronic non-bacterial osteomyelitis (predominantly affecting children) was an indication that would be reasonable to consider for widened access, on the basis of multiple approved NPPA applications and emerging evidence for adalimumab (Cheetham et al. Rheum. 2025;64(Suppl_3):P097).

12.31. The Committee considered that while the evidence supported biosimilar-to-biosimilar changes for adalimumab without loss of efficacy or increased AEs, patient-reported experience can be suboptimal without sufficient communication and practical support to manage implementation of a non-medical change.

12.31.1. The Committee was made aware of a cohort in the UK in which a mandated switch to an adalimumab biosimilar led to about half of all switchers reverting back to the reference adalimumab, commonly citing AEs or loss of efficacy as a reason (Holden et al Rheum. 2023;62(Suppl 2):P010). Members considered this pattern was consistent with a "nocebo" effect (ie a phenomenon where negative expectations about a treatment or intervention lead to worsened outcomes, even if the treatment itself is not having a different impact or is beneficial) and noted that as a consequence, expected cost savings were not realised when many reverted.

12.31.2. The Committee acknowledged New Zealand's experience showing lower patient satisfaction after a mandated change to a biosimilar despite preserved efficacy and safety (Gasteiger et al. ACR Open Rheumatol. 2024;6:64-71). The Committee noted that the authors reported issues including sharps disposal, alcohol wipes, device training, and reduced patient-support services, with mean satisfaction of about 6/10 post-transition compared with pre-transition ratings often 8–9/10 for several support elements.

12.31.3. Members considered that patient-reported experience was particularly relevant in the context of a change from a reference biologic associated with a comprehensive supplier support package to a biosimilar with a lesser extent of patient support provided by the supplier.

12.32. The Committee noted that the currently funded adalimumab biosimilar (Amgevita) is a citrate-free product. Members considered the New Zealand paediatric IBD clinicians' perspective that changing to a citrate-free biosimilar reduced injection-site pain and was viewed positively. Members considered that a citrate-free adalimumab formulation would be a particularly important consideration for future biosimilar procurement, especially if intended to be funded for treatment for children and for use in the community.

*Suitability, clinical service and implementation considerations*

12.33. The Committee considered that it would be important for communications regarding any future non-medical change from biosimilar to biosimilar to acknowledge that the driver for this change was fiscal reasons and potential widened access.

12.34. The Committee noted that broad patient-support elements (eg device training, sharps disposal etc, as described for adalimumab) differ between reference biologics and biosimilar products. The Committee considered that this would be an important consideration as these differences can materially affect patient-reported experience, persistence on therapy, transition success and cost outcomes.

12.35. The Committee considered that successful procurement should be coupled with change-management, liaison with Health New Zealand | Te Whatu Ora regarding service impacts, and consumer engagement when planning biosimilar changes.

12.36. The Committee considered that biosimilar-to-biosimilar changes may be associated with clinical service impacts for oncology and infusion settings, such as requirements for disclosure and re-consent with potential increases in visits during transition periods. Members reported (anecdotally) that there had been a tangible, time-limited increase in visits during a prior oncology biosimilar change.

12.37. The Committee considered that there were differing levels of clinician comfort with changing from reference biologics to biosimilars across specialties and that this could similarly apply to biosimilar-to-biosimilar changes. Members considered that clear communication to clinicians and other healthcare professionals (ie nurses and pharmacists) would support evidence-based clinical conversations and implementation, minimising the potential for nocebo effects.

12.38. The Committee considered that specific strategies for minimising nocebo effects and supporting patient experience could include early and positive framing, empathetic and validating communication, shared decision-making, self-affirmation techniques, practical device training, and ensuring availability of sharps bins and alcohol wipes. The Committee considered that it would also be important to clearly emphasise that a

biosimilar is very similar to a reference biologic during implementation of a biosimilar-to-biosimilar change.

*General*

12.39. The Committee considered that, if Pharmac were to consider biosimilar-to-biosimilar changes for other biologics in future, inclusion of patient-reported outcomes in future evidence packages would be useful, as would including abstracts and grey literature from areas with limited data.

12.40. Members considered that the Consumer Advisory Committee could provide valuable updated input on messaging and consumer-facing materials (such as information about biological and biosimilar medicines on Pharmac's website and the Factsheet: Biological and biosimilar medicines) ahead of any proposed biosimilar-to-biosimilar change. Members considered it important to include clear explanations that biosimilars are similar to the reference product and guidance to avoid misattributing background symptoms to brand changes.

## 13. Avacopan (Tavneos) for ANCA-associated vasculitis

### Application

13.1. The Committee reviewed the application for avacopan in the treatment of ANCA-associated vasculitis, to be used in conjunction with rituximab or cyclophosphamide regimen for up to 12-months.

13.2. The Committee noted a clinician application (April 2024) and a supplier application (March 2025), each proposing different target populations, as reflected in each Special Authority criteria listed below. The Committee noted that the clinician application focused on a narrower group at higher risk of steroid-related harm, while the supplier application proposed a broader population: adults (≥18 years) with severe disease defined by Birmingham Vasculitis Activity Score version 3 (BVAS), including at least one major or three non-major manifestations, or two renal manifestations (haematuria and proteinuria).

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

### Recommendation

13.4. The Committee **recommended** that avacopan for the treatment of ANCA-associated vasculitis be listed with a **high priority**, subject to the following Special Authority criteria:

> **Initial application – ANCA associated vasculitis**
> Application from any relevant practitioner. Approvals valid for 6 months.
> All of the following:
> 1. Patient has been diagnosed with ANCA associated vasculitis; and
> 2. Patient has organ or life-threatening disease; and
> 3. Avacopan is to be given in combination with either cyclophosphamide or rituximab induction therapy.
>
> **Renewal application – ANCA associated vasculitis**
> Application from any relevant practitioner. Approvals valid for 6 months.
> All of the following:
> 1. Patient has received clinically significant benefit from treatment; and
> 2. A maximum of 12 months treatment is to be given inclusive of induction and maintenance.

13.5. The Committee **recommended** that avacopan for the treatment of ANCA-associated vasculitis in a subset who are at the highest risk of adverse outcomes from high-dose steroid use be listed with a **high priority**, subject to the following Special Authority criteria:

**Initial application – ANCA associated vasculitis**
Application from any relevant practitioner. Approvals valid for 6 months.
All of the following:

1. Patient has been diagnosed with ANCA associated vasculitis; and
2. Patient has organ or life-threatening disease; and
3. Avacopan is to be given in combination with either cyclophosphamide or rituximab induction therapy; and
4. Any of the following:
    1. eGFR at baseline between 15-30 ml/min; or
    2. Poorly controlled diabetes; or
    3. Obesity (BMI >30); or
    4. Age over 65 or established osteoporosis; or
    5. Any significant mental health issue where corticosteroid avoidance is advisable.

**Renewal application – ANCA associated vasculitis**
Application from any relevant practitioner. Approvals valid for 6 months.
All of the following:
1. Patient has received clinically significant benefit from treatment; and
2. A maximum of 12 months treatment is to be given inclusive of induction and maintenance.

13.7. The Committee, in making these recommendations, considered the following:

13.7.1. High health need of individuals with ANCA-associated vasculitis.

13.7.2. The suitability of an oral treatment option compared with intravenous therapies.

13.7.3. The potential to reduce long-term healthcare costs by decreasing steroid-related complications, hospitalisations, and renal replacement therapy rates.

13.7.4. Pharmac could consider targeting funding to the narrower population of individuals at the highest risk of adverse outcomes from high-dose steroid use as a means to maximise potential benefit of avacopan use in a cost-constrained environment.

## Discussion

*Patient lived experience*

13.8. The Committee acknowledged the consumer submissions and expert commentary that fatigue and steroid-related impacts materially affect people's ability to work and participate in daily life. Committee Members wished to express their sincere gratitude to those who took the time to contribute.

*Invited experts*

13.9. Dr. Vicki Quincey and Dr. Ravi Suppiah attended the discussion as Observers – Invited Experts. Drs. Quincey and Suppiah left the meeting before the recommendation was made.

*Māori impact*

13.10. The Committee discussed the impact of funding avacopan for the treatment of ANCA-associated vasculitis on Māori health areas of focus | Hauora Arotahi and Māori health outcomes.

13.11. The Committee noted that there was no new evidence of increased prevalence of ANCA-associated vasculitis in Māori and noted a lack of specific research and awareness regarding how this condition impacts Māori.

13.12. The Committee noted that while there is no direct evidence to suggest a higher incidence of ANCA-associated vasculitis in Māori populations, renal disease is a significant health burden in these communities. Committee Members considered that improvements in eGFR, such as those observed with avacopan, may offer hidden cost benefits by delaying

progression to end-stage kidney disease and reducing the need for dialysis and renal transplantation, which carry substantial long-term healthcare costs.

13.12.1. The Committee considered that Māori and Pacific peoples may be overrepresented in the target population for avacopan if the clinician-proposed criteria are adopted, due to higher prevalence of risk factors such as reduced eGFR, poorly controlled diabetes, and obesity.

*Populations with high health needs*

13.13. The Committee discussed the health need(s) of ANCA-associated vasculitis among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs.

13.13.1. The Committee noted the substantial impact of kidney disease and diabetes in Māori and Pacific peoples and considered that steroid-sparing and renal benefits from avacopan may therefore be particularly important for these populations.

*Background*

13.14. The Committee noted in February 2025 PTAC reviewed a request to widen access to rituximab, extending its use from induction therapy to include maintenance therapy for ANCA-associated vasculitis.

13.14.1. At the time, the Committee recommended that rituximab for maintenance therapy of ANCA-associated vasculitis be listed with a high priority with no restriction on treatment duration, subject to special authority criteria. In making this recommendation the Committee considered the following:

13.14.2. The high health need of people with life- or organ-threatening ANCA-associated vasculitis and the impact of disease relapses on individuals and their whānau.

13.14.3. The moderate quality of the available evidence that rituximab reduces the rate of relapse compared to comparator treatment(s) or placebo.

13.15. The Committee noted that rituximab is funded as induction therapy under Special Authority for ANCA-associated vasculitis, and is currently under consideration as maintenance therapy.

13.16. The Committee noted the existing treatments for ANCA-associated vasculitis in New Zealand typically involve induction with corticosteroids with either cyclophosphamide or rituximab, followed by maintenance with azathioprine and tapering corticosteroids (Chua et al. Intern Med J. 2024;54:1097-105).

13.16.1. The Committee noted that the alternatives for those unable to take azathioprine include mycophenolate (MMF) and methotrexate (MTX).

13.16.2. The Committee also noted ANCA-associated vasculitis is a relapsing-remitting condition, often resulting in high cumulative steroid exposure.

13.17. Members acknowledged that prednisone is associated with significant adverse effects. Committee Members further noted that clinicians treating individuals with ANCA-associated vasculitis frequently manage long-term complications of prednisone use, and that steroid sparing therapies are therefore of high clinical interest.

13.17.1. Members considered that while steroid-sparing is often undervalued in treatment assessments, it holds particular importance for patients with ANCA-associated vasculitis due to their vulnerability to steroid-related harm. Members noted that maintenance therapy with rituximab may offer substantial long-term benefits, including reduced relapse rates without the need for ongoing prednisone.

*Health need*

13.18. The Committee noted ANCA-associated vasculitis is a rare, relapsing-remitting, organ- and life-threatening condition with risk of end-stage kidney disease and substantial treatment-related harms from high-dose and cumulative glucocorticoid exposure. The

Committee noted that the health need of those with ANCA-associated vasculitis has been previously described by PTAC in February 2025.

13.19. The Committee noted that ANCA-associated vasculitis has an incidence of 0.4–24 cases per million person-years, with an average age at diagnosis of 40–50 years. The Committee noted New Zealand data indicate a five-year prevalence of 152 cases per million for granulomatosis with polyangiitis (GPA) and 58 cases per million for microscopic polyangiitis (MPA).

13.20. The Committee noted that, despite currently available treatments for ANCA-associated vasculitis, there remains an unmet health need. The Committee noted that existing therapies rely heavily on the frequent use of high-dose corticosteroids, which are associated with significant adverse effects.

13.20.1. The Committee considered that even if funding for rituximab were expanded to include maintenance therapy for ANCA-associated vasculitis, an unmet health need remains. The Committee noted that remission rates with rituximab and avacopan are approximately 70–75% (Jayne, D et al. N Engl J Med. 2021;384:599-609), indicating that a proportion of patients may still not achieve or sustain remission.

*Health benefit*

13.21. The Committee noted avacopan is a selective antagonist of the complement 5a receptor (C5aR, also called CD88) that competitively inhibits C5a interaction, including blocking neutrophil chemo-attraction and activation. The Committee noted avacopan reduces C5a's pro-inflammatory effects, modulates neutrophil activity, and decreases vascular inflammation and permeability.

13.21.1. The Committee noted the recommended dose of avacopan is 30 mg orally, twice daily.

13.21.2. The Committee noted avacopan is initiated with either rituximab or cyclophosphamide to induce remission. The Committee noted treatment is continued for up to 12-months in combination with standard of care.

13.21.3. The Committee considered that individuals would receive avacopan usually as first-line treatment, however, as the trial data only assessed 12-months of total treatment, there remain uncertainties regarding the need for and outcomes of retreatment with avacopan.

13.22. The Committee noted the ADVOCATE trial, a phase 3, randomised (1:1), double-blind, active-controlled, double-dummy study comparing avacopan with a prednisone-based regimen, both in combination with cyclophosphamide or rituximab (Jayne, D et al. N Engl J Med. 2021;384:599-609).

13.22.1. The Committee noted that inclusion criteria required an estimated eGFR of at least 15 ml/min and either one major or three non-major BVAS items, or two renal items (haematuria and proteinuria). The Committee noted that all participants received cyclophosphamide followed by azathioprine, or rituximab (four infusions over three weeks), with primary endpoints assessed at 26 and 52 weeks.

13.22.2. The Committee noted the first primary end point was remission, defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) measured at week 26 and no glucocorticoid use in the previous four weeks. The Committee noted the second primary end point was sustained remission, defined as remission at both weeks 26 and 52 (both end points were tested for non-inferiority and superiority).

13.22.3. The Committee noted the mean BVAS at baseline was 16 in both groups. The Committee noted remission at week 26 was observed in 120 of 166 participants (72.3%) receiving avacopan and in 115 of 164 participants (70.1%) receiving prednisone (estimated common difference, 3.4 percentage points; 95% confidence interval [CI], -6.0 to 12.8; $p<0.001$ for non-inferiority; $p=0.24$ for superiority).

13.22.4. The Committee noted sustained remission at week 52 was observed in 109 of 166 participants (65.7%) receiving avacopan and in 90 of 164 participants (54.9%) receiving prednisone (estimated common difference, 12.5 percentage points; 95% CI, 2.6 to 22.3; p<0.001 for non-inferiority; p=0.007 for superiority).

13.22.5. The Committee noted that the effects of glucocorticoid treatment were assessed using both the Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS) and the Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS). The Committee noted that participants receiving avacopan showed more favourable outcomes on both measures compared to those receiving corticosteroids, as expected.

13.22.6. The Committee noted that at week 52, the least-squares mean change in eGFR from baseline was 7.3 mL/min/1.73 m² in the avacopan group and 4.1 mL/min/1.73 m² in the prednisone group (difference 3.2 mL/min/1.73 m²; 95% CI, 0.3 to 6.1). The Committee also noted among participants with stage 4 kidney disease (baseline eGFR <30 mL/min/1.73 m²), the mean change was 13.7 mL/min/1.73 m² with avacopan and 8.2 mL/min/1.73 m² with prednisone (difference 5.6 mL/min/1.73 m²; 95% CI, 1.7 to 9.5). The Committee acknowledged that two participants in the avacopan group and four in the prednisone group required dialysis during the treatment period.

13.22.7. The Committee noted that health-related quality of life improved in both groups, with greater gains observed in participants receiving avacopan. The Committee noted improvements were reported across the 36-Item Short Form Health Survey (SF-36) domains and the EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) scores, consistent with sustained remission outcomes. The Committee also noted that the hazard ratio for relapse after remission with avacopan versus prednisone was 0.46 (95% CI, 0.25 to 0.84).

13.22.8. The Committee noted that adverse events were common in both groups, occurring in nearly all participants. Serious adverse events were reported in 23.5% of participants receiving avacopan and 25.0% receiving prednisone, while life-threatening events occurred in 4.8% and 8.5%, respectively. The Committee noted that serious infections were the most frequent severe events, affecting 13% of participants in the avacopan group and 15% in the prednisone group. The Committee noted that longer-term effects of avacopan are not currently known.

13.22.9. The Committee noted that cumulative glucocorticoid exposure was substantially lower in the avacopan group (mean total prednisone-equivalent dose 1,676 mg; 5 mg/patient/day) compared with the prednisone group (3,847 mg; 13 mg/patient/day). The Committee also noted that non-protocol use of additional immunosuppressants for worsening or relapse occurred in 17.5% of participants receiving avacopan and 22.0% receiving prednisone.

13.22.10. The Committee noted that non-protocol use of additional immunosuppressants was lower in the avacopan group compared with the prednisone group across both time periods. From weeks 1–26, any additional immunosuppressant was used in 8.4% of participants receiving avacopan and 9.8% receiving prednisone. From week 27 to the end of treatment, use increased to 11.4% and 15.2%, respectively, with rituximab being the most common agent in both groups.

13.22.11. The Committee noted that disease severity in the ADVOCATE trial was considered similar to that seen in New Zealand. Differences included a higher proportion of participants over 65 years in New Zealand and greater ethnic diversity (17.8% Māori and 6.9% Pacific peoples compared with 84.3% European in the trial). The Committee noted that no analysis of treatment effects by ethnicity was undertaken. These differences were considered unlikely to materially affect treatment response, but members highlighted the importance of equity considerations for Māori and Pacific peoples.

13.22.12. The Committee considered the potential imbalance in corticosteroid use at baseline between treatment arms in the pivotal trial. Members noted that although eligibility criteria required steroid doses to be reduced prior to trial entry, and patients with high cumulative steroid exposure were excluded, the number of patients using steroids during the screening period was higher in the prednisone group. However, total per-patient prednisone-equivalent doses were not substantially different between groups.

13.22.13. Committee Members noted that although the improvement in renal function observed in the ADVOCATE study may appear modest, even small increases in eGFR can have significant clinical implications, particularly in individuals with severely impaired kidney function. Committee Members also noted that avacopan was associated with reduced infection risk compared to the risk in those receiving prednisone, which is particularly important given that infection can negatively impact renal function and is a major cause of mortality in this condition. The Committee considered that while the numerical differences may be small, the long-term impact on individual outcomes and healthcare costs could be substantial.

13.22.14. The Committee considered that avacopan offers potential health benefits for people with ANCA-associated vasculitis in Aotearoa New Zealand, including better tolerability, reduced steroid exposure, improved health-related quality of life, and likely superior renal outcomes.

13.23. The Committee noted the CLEAR trial, a phase 2, randomised, double-blind, placebo-controlled study evaluating avacopan as a strategy to reduce or replace glucocorticoid use in ANCA-associated vasculitis (Jayne, D et al. J Am Soc Nephrol. 2017;28(9):2756-67).

13.23.1. The Committee noted that 67 participants with newly diagnosed or relapsing ANCA-associated vasculitis were randomised (1:1:1) to receive either prednisone starting at 60 mg (control), avacopan 30 mg twice daily plus prednisone 20 mg, or avacopan 30 mg twice daily without prednisone. The Committee also noted that all participants also received cyclophosphamide or rituximab as background therapy.

13.23.2. The Committee noted that the treatment duration was 12 weeks, with the primary endpoint being the proportion of participants achieving a ≥50% reduction in BVAS at week 12 without any worsening in any body system.

13.23.3. The Committee noted that clinical response at week 12 was achieved in 70% of participants in the control group, 86.4% in the avacopan plus reduced-dose prednisone group (difference from control 16.4%; 90% CI, −4.3 to 37.1; *P*=0.002 for non-inferiority), and 81% in the avacopan monotherapy group (difference from control 11.0%; 90% CI, −11.0 to 32.9; *P*=0.01 for non-inferiority).

13.23.4. The Committee noted that avacopan was generally well tolerated and appeared effective in reducing or replacing high-dose glucocorticoids without compromising disease control.

13.23.5. The Committee noted that adverse events occurred in 91% of participants in the prednisone-only group, 86% in the avacopan plus prednisone group, and 96% in the avacopan-only group.

13.23.6. The Committee noted that participants in the CLEAR trial were younger than those typically seen in New Zealand (mean age 57–59 years) and all identified as European, limiting generalisability to the New Zealand population.

13.24. The Committee noted the CLASSIC trial, a phase 2, randomised, double-blind, placebo-controlled study evaluating the safety and preliminary efficacy of avacopan in ANCA-associated vasculitis (Merkel, P et al. ACR Open Rheumatol. 2020;2(11):662-71)

13.24.1. The Committee noted that 42 participants with newly diagnosed or relapsing ANCA-associated vasculitis were randomised to receive avacopan 30 mg twice

daily plus standard of care, avacopan 10 mg twice daily plus standard of care, or standard of care alone, for a treatment duration of 12 weeks.

13.24.2. The Committee noted that primary endpoints included the proportion of participants achieving a ≥50% reduction in BVAS at day 85, rapid reduction of BVAS to 0 by day 29 sustained through day 85, change in Vasculitis Damage Index (VDI), renal response (haematuria and albuminuria), and health-related quality of life.

13.24.3. The Committee noted that BVAS response rates were high across all arms: 11 of 13 participants in the standard of care group, 11 of 12 in the avacopan 10 mg group, and 12 of 15 in the avacopan 30 mg group. The Committee noted increases in mean VDI were greater in the standard of care group (0.3) compared with the avacopan groups (0.1), suggesting less accrued damage with avacopan.

13.24.4. The Committee noted that participants receiving avacopan reported greater improvements in health-related quality of life compared with those receiving standard of care alone. The Committee noted based on the Short Form 36 version 2 (SF-36v2), improvements were observed in bodily pain, vitality, mental health, physical function and emotional role, with benefits evident as early as four weeks.

13.24.5. The Committee also noted that participants receiving avacopan reported a greater perceived improvement in overall health compared with one year prior, based on the Health Transition domain.

13.24.6. The Committee noted EQ-5D-5L visual analogue scale (VAS) scores and health index values increased across all groups, with the largest VAS improvement in the avacopan 30 mg arm (61.4% vs 44.1% with standard of care and 39.7% with avacopan 10 mg). Health index values increased by 6.4% with standard of care, 9.6% with avacopan 10 mg, and 7.2% with avacopan 30 mg.

13.25. The Committee noted a post-hoc analysis of the ADVOCATE trial evaluating the efficacy and safety of avacopan in participants aged 65 years and older (Geetha, D et al. Rheumatology (Oxford). 2025;64(6):3863-71). The Committee noted that 160 participants were included, comprising 109 aged 65–74 years and 51 aged ≥ 75 years.

13.25.1. The Committee noted that remission rates at week 26 were similar between avacopan and prednisone taper across both age groups, with rates of 71.7% versus 69.4% in participants aged 65–74 years, and 73.1% versus 72.0% in those aged 75 years and older.

13.25.2. The Committee noted that sustained remission at week 52 was higher with avacopan compared with prednisone taper, with rates of 65.0% versus 55.1% in the 65–74 age group, and 65.4% versus 56.0% in the ≥75 age group.

13.25.3. The Committee noted that improvements in estimated glomerular filtration rate (eGFR) and health-related quality of life were observed in both treatment groups, with trends similar to those seen in the overall ADVOCATE population.

13.25.4. The Committee noted that adverse event rates were comparable between avacopan and prednisone taper across both age groups.

13.26. The Committee noted a subgroup analysis of the ADVOCATE trial evaluating the efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving background induction therapy with rituximab (Geetha, D et al. Ann Rheum Dis. 2024;83(2):233-32).

13.26.1. The Committee noted that of the 330 patients enrolled in the trial, 214 (64.8%) received rituximab, with 107 patients each in the avacopan and prednisone taper groups. The mean age was 59.8 years, 76.2% had renal vasculitis, and 58.4% were newly diagnosed.

13.26.2. The Committee noted that rates of remission and sustained remission at weeks 26 and 52, respectively, were approximately 5 percentage points higher in both the avacopan and prednisone groups among rituximab-treated participants compared

with the overall trial cohort, suggesting a modest additive benefit of rituximab to both treatment arms.

13.27. The Committee was made aware of a post-hoc analysis of the ADVOCATE trial evaluating outcomes in participants with ANCA-associated vasculitis and severe renal dysfunction at baseline (eGFR ≤20 ml/min/1.73 $m^2$) (Cortazar, et al. Kidney Int Rep. 2023;8(4):860-70).

13.27.1. The Committee noted that 16% of patients in the avacopan group and 14% in the prednisone group had severe renal impairment at baseline, and that eGFR improved significantly more in the avacopan group (16.1 ml/min/1.73 $m^2$) than in the prednisone group (7.7 ml/min/1.73 $m^2$) at week 52 (p = 0.003).

13.27.2. The Committee noted that 41% of patients in the avacopan group achieved a ≥2-fold increase in eGFR from baseline, compared with 13% in the prednisone group (p = 0.030), and that more patients in the avacopan group reached eGFR thresholds above 20, 30, and 45 ml/min/1.73 $m^2$.

13.28. The Committee considered that the evidence supporting avacopan for ANCA-associated vasculitis is based on one pivotal phase 3 study, along with two smaller phase 2 studies and several post-hoc analyses. The Committee noted that the pivotal study was sponsor-initiated and appears to have been well designed and conducted providing a reasonable level of certainty within the context of a rare disease.

13.28.1. The Committee considered that the supplier-estimated 10-point decrease in eGFR with each relapse appears reasonable, based on evidence suggesting a strong relationship between relapse frequency and progression to end-stage kidney disease. Members noted that published data indicate a deterioration in eGFR of 10–20 ml/min/1.73 $m^2$ per relapse (Slot, et al Kidney Int. 2003;63(2):670-7), supporting the validity of the estimate.

*Suitability*

13.29. The Committee noted that avacopan is an oral therapy requiring twice-daily dosing with food, with each dose consisting of three 10 mg capsules. The Committee also noted that avacopan has a shelf-life of 36 months when stored below 30°C.

13.30. The Committee noted that avacopan is administered orally and does not require travel to hospital, offering convenience benefits over intravenous treatments. However, Members considered that the extent of these non-clinical advantages would depend on the place of avacopan in the treatment algorithm. No other significant non-clinical differences were identified compared to current comparators.

13.31. The Committee noted the avacopan regimen should not significantly increase tablet burden, given that those with ANCA-associated vasculitis are already receiving multiple concurrent medications.

*Cost and savings*

13.32. The Committee acknowledged that the supplier's cost utility analysis (CUA) model associated the funding of avacopan with a reduction in hospital costs related to end stage renal disease and adverse events and infections, and a reduction in hospital resource use associated with relapse-related hospitalisations.

13.33. Committee Members considered the substantial cost difference between avacopan and rituximab, noting that rituximab maintenance therapy may offer comparable clinical benefits, particularly in reducing steroid use, at a significantly lower cost. Members noted that while avacopan may be effective, the ability to treat a larger number of individuals with rituximab maintenance for the same expenditure likely presents a more cost-efficient option.

13.34. The Committee considered that there may be benefit in looking at the disutility of steroid use across the disease area rather than using the utility data directly from the trial which may underestimate the harm caused by long-term steroid use.

13.35. The Committee considered that the split of cyclophosphamide and rituximab induction therapy in the ADVOCATE trial is now more reflective of current practice in New Zealand, particularly from a renal perspective. Members noted that the previously reported 8% rituximab usage is outdated, and that current induction use is likely closer to the trial proportions. As a result, the Committee considered the expected incremental benefit of avacopan observed in the trial may be more applicable to the New Zealand treatment context.

*Funding criteria*

13.36. The Committee noted the two different Special Authority criteria proposed from the Clinician and Supplier applications. The Committee acknowledged that the clinician-recommended criteria were designed to support the best use of avacopan in a cost-constrained environment, should funding be approved.

13.37. The Committee further noted that the rationale for including a baseline eGFR of 15–30 mL/min was based on trial data showing the greatest percentage and most clinically meaningful improvement in eGFR at 12 months among participants in this range. Members noted a 5 mL/min improvement in eGFR in this group could have prognostic implications, particularly in reducing the future need for renal replacement therapy.

13.38. The Committee noted that the clinician's recommendations for criteria points 4.2 to 4.5 were aimed at preventing harm in individuals with ANCA-associated vasculitis who are at highest risk of adverse outcomes from high-dose steroid use.

*Summary for assessment*

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

<table>
<tr><td>Population</td><td>Supplier-proposed target group:<br>Newly diagnosed or relapsed adults (18 years and over) with severe disease, diagnosed or relapsed GPA or MPA defined as:<ul><li>At least one major manifestation</li><li>Or three non-major manifestations</li><li>Or at least two renal manifestations of haematuria and proteinuria (using the validated Birmingham Vasculitis Activity Score, version 3)</li></ul>Staff interpret this population to be those with organ-threatening or life-threatening disease, aligning with the currently funded AAV populations.</td><td>Clinician proposed target group:<ul><li>eGFR at baseline between 15-30 ml/min</li><li>Poorly controlled diabetes</li><li>Obesity (BMI >30)</li><li>Age over 65 or established osteoporosis</li><li>Any significant mental health issue where corticosteroid avoidance is advisable.</li></ul>Staff interpret this to be a subset of the supplier-targeted population, targeting those with a higher health need and/or greater potential to benefit from reduced steroid use.</td></tr>
<tr><td>Intervention</td><td colspan="2">Avacopan (add-on therapy) 30 mg twice daily:<br>1. Up to week 21 ie the first six-months (roughly aligning with SoC ‘induction’ period):<br>2. Weeks 22 onwards, once in remission, continued for up to 12 in total months (roughly aligning with SoC ‘maintenance’ period):<br><br>In combination with standard of care (SoC) as follows:<br>1. SoC induction:<br>Cyclophosphamide OR rituximab<br>Used in combination with oral/IV corticosteroids, with dose and tapering based on need (eg vasculitis, renal insufficiency, worsening of disease)<br>2. SoC maintenance:<br>Azathioprine OR methotrexate [OR rituximab maintenance*, if funded))<br>In combination with corticosteroid tapering[#]<br><br>*Rituximab maintenance has been included as a potential component of future treatment paradigms. While it is not currently funded, it was recommended with a high priority [PTAC, Feb 2025]. Rituximab was not used beyond 4 weeks in the ADVOCATE trial.<br>[#]Mandatory prednisone taper in ADVOCATE trial, designed to discontinue prednisone by Week 21.</td></tr>
<tr><td>Comparator(s)<br>(NZ context)</td><td colspan="2">SoC induction and maintenance as above, but with higher corticosteroid doses (oral and total) and longer duration of corticosteroids during 21-week induction period in all patients.</td></tr>
</table>

| | |
|---|---|
| **O**utcome(s) | 1. Improvement in HRQOL through reduced overall corticosteroid use<br>2. Larger improvement in eGFR levels compared to current standard of care (with consequent improvement in quality of life and longevity through delayed progression of renal failure)<br>3. Increased likelihood of sustained remission at 52 weeks<br>4. Reduced negative impacts of corticosteroid use<br><br>**Outcomes vs current SoC**<br><br>Disease progression<br><br>• non-inferior remission at 26 weeks<br>• superior sustained remission at 52 weeks<br>• reduced relapse<br><br>Improved renal function (eGFR)<br><br>Reduction in CS exposure up to week 21 (similar exposure weeks 22 to 52)<br><br>Reduction in CS side effects and healthcare costs associated with their management<br><br>Improved QoL<br><br>**Outcomes vs SoC including rituximab maintenance**<br><br>There is no evidence to inform. |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

## 14. Inclisiran for heterozygous familial hypercholesterolemia

### Application

14.1. The Committee reviewed the application for inclisiran in the treatment of heterozygous familial hypercholesterolemia.

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

### Recommendation

14.3. The Committee **recommended** that inclisiran for heterozygous familial hypercholesterolemia be listed with a **high priority**, subject to the following Special Authority criteria:

Initial application – heterozygous familial hypercholesterolemia (HeFH)
Applications from any relevant practitioner. Approvals valid for 12 months.
All of the following:

1. Treatment will be used in conjunction with dietary therapy and exercise; and

2. Patient has a diagnosis of heterozygous familial hypercholesterolemia confirmed by either:
   2.1. Genetic testing; or
   2.2. A Dutch Lipid Clinic Network Score of at least 6; and
3. Either:
   3.1. Patient has been treated with maximum tolerated doses of statin for three or more months; or
   3.2. Statins are not able to be tolerated or are contraindicated; and
4. Patient has been treated with ezetimibe for three or more months; or
   4.1. Ezetimibe is not able to be tolerated or is contraindicated; and
5. Either:
   5.1. Both:
      5.1.1. Patient has ASCVD; and
      5.1.2. Patient is experiencing persistently elevated LDL-C ≥1.4 mmol/L; or
   5.2. Patient is experiencing persistently elevated LDL-C ≥4.5 mmol/L (in the absence of ASCVD)

Renewal – heterozygous familial hypercholesterolemia (HeFH)
Applications from any relevant practitioner. Approvals valid for 12 months.
Both:
1. Treatment remains appropriate; and
2. Patient is benefitting from treatment.

14.5. In making their recommendation, the Committee considered:

14.5.1. Despite access to funded treatments, there is still an unmet health need in the HeFH population and alternative lipid lowering therapies are needed.

14.5.2. There is a therapeutic benefit of significant LDL-C reduction associated with the use of inclisiran and potentially reduces major cardiovascular events.

14.5.3. The infrequent subcutaneous administration method would provide a suitability benefit compared to the currently funded daily orally administered treatments for some individuals.

14.5.4. The LDL-C thresholds proposed for the Special Authority Criteria for inclisiran will need to be confirmed following further clinical advice from the Cardiovascular Advisory Committee.

## Discussion

*Māori impact*

14.6. The Committee discussed the impact of funding inclisiran for the treatment of heterozygous familial hypercholesterolemia (HeFH) on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. The Committee considered that there is no evidence to indicate that Māori have a higher prevalence of HeFH than non-Māori but in general experience worse coronary heart disease-related health outcomes, access to cardiac health care, and thereby, are often underdiagnosed.

*Populations with high health needs*

14.7. The Committee discussed the health need(s) of HeFH among Māori, Pacific peoples, disabled peoples including tāngata whaikaha, Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding inclisiran and considered:

14.7.1. There is no evidence to indicate that Pacific people have a higher prevalence of HeFH than non-Pacific but in general experience worse coronary heart disease-related health outcomes and reduced access to cardiac health care, and thereby, are often underdiagnosed in the context of cardiac disease.

*Background*

14.8. Pharmac has previously considered two PCSK-9 inhibitors; evolocumab and alirocumab. The evolocumab funding application was declined in 2018 due to a lack of evidenced mortality benefit, high cost and a paucity of primary prevention evidence. Alirocumab was recommended with high priority by the Cardiovascular Advisory Committee in 2019 for people with HeFH but the medicine has subsequently been discontinued by the supplier (Sanofi) in Australia and New Zealand.

14.9. The Committee noted that the supplier of inclisiran has also submitted an application for inclisiran in the treatment of atherosclerotic cardiovascular disease that will receive clinical advice at a later date.

*Health need*

14.10. The Committee noted that HeFH is associated with high low-density lipoprotein cholesterol (LDL-C) levels, ranging from 4.5mmol to 12mmol. There are three possible mutations that cause the disease, with the loss of function in LDL-C receptors making up 90% of cases (Farias et al. 2023;109:1486-93).

14.11. The Committee noted that HeFH is a relatively common disease, with incidence estimates ranging between 1 in 250 to 1 in 500 people, approximately 10-20,000 people in New Zealand (Scott et al. Research Review NZ, 2019).

14.12. The Committee noted that HeFH is an asymptomatic condition until a heart attack event or death, and is normally diagnosed after a heart attack event, with less than 2% of individuals in the expected HeFH population in New Zealand identified via proactive testing using the Dutch Lipid Clinic Network Score (DLCNS) or genotyping (although the latter is uncommon) (McGowan et al. JAHA. 2019;8:e013225; Scott et al., 2019). The Committee noted that the DLCNS uses seven factors to identify HeFH, including LDLC levels, family history, clinical history, and physical examination.

14.13. The Committee noted that HeFH increases vascular disease risk (30-50% chance of a fatal or non-fatal myocardial infarction (MI) by the age of 60) (Sturm et al. J Am Coll Cardiol. 2018;72:662-80). People with HeFH experience higher mortality due to MI, cerebrovascular accident (CVA), and cardiovascular disease (CVD) at a younger age than the general population (Ference et al. Eur Heart J. 2017;38:2459-72; Sturm et al., 2018).

14.14. The Committee noted that statins and ezetimibe are the pharmaceutical treatments currently funded for this population. Statin treatment is considered moderately effective and improves cumulative event-free survival, however a large proportion of individuals with HeFH do not achieve LDL cholesterol targets and remain at an increased risk of cardiac events (Nordestgaard et al. Eur Heart J. 2020;41:4517). The Committee considered it likely that most people with HeFH are not on statin treatment due to the underdiagnosis of HeFH. Most secondary prevention individuals do not reach target LDL-C levels because of this, and experience clinical inertia (Underberg et al. Postgrad Med. 2022;134:752-62).

14.15. The Committee noted that despite treatment with statins and ezetimibe, the majority of people with HeFH do not reach LDL-C targets (<2.5 mmol/l in patients without established CVD and <1.8 mmol/l in patients with CVD) as established in the 2016 European Guidelines for Cardiovascular disease prevention, and that the prevalence of statin intolerance is 9.1% (Law et al. BMJ. 2003;326:1423; Schreuder et al. Atherosclerosis. 2023;384:117117; Bytyçi et al. Eur Heart J. 2022;43:3213-23). The Committee considered that due to a lack of treatment options and a high risk of HeFH related morbidity or mortality, that there is unmet health need in the HeFH population.

14.16. The Committee noted that lipid apheresis (LA) treatment for HeFH is uncommon, and not generally performed in New Zealand as it is resource intense and expensive. The Committee discussed a LA audit publication, which reported 16 individuals treated with LA in New Zealand and Australia, eight of which had HeFH. The individuals were treated with LA every 2-4 weeks. Four of the eight people with HeFH were able to stop LA after initiating treatment with PCSK-9 inhibitors (Page et al. J Clin Apher. 2021;36:48-58).

14.17. The Committee noted that there is a log-linear association in LDL-C and the risk of cardiovascular disease as reported in meta-analyses of Mendelian randomisation studies, prospective epidemiologic cohort studies, and randomised trials (Ference et al., 2017). The Committee considered that this indicated that benefit is equated to the amount by which LDL-C is lowered over a duration of time, with earlier and sustained treatment resulting in better prognosis.

14.18. The Committee noted that inclisiran is a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor. The inhibition of PCSK9 reduces LDL cholesterol by prolonging the lifespan of LDL receptors, enabling receptors to remove LDL cholesterol from the bloodstream (Corral P, Arq Bras Cardiol. 2014;102:e5-8).

*Health benefit*

14.19. The Committee noted that there are three clinical trials of high relevance for the treatment of HeFH with inclisiran, ORION-9, ORION-10, and ORION-11. The Committee noted that the trials were of relatively short duration (18 months), and the primary outcome identified was the percentage of change in LDL-C from baseline measurement until day 510 in the trial. Other outcomes (including major cardiovascular events (MACEs) were exploratory and non-powered. The Committee considered that the ORION trials were of robust quality, and that LDL-C is an evidenced surrogate marker that is appropriate for this population. The Committee also noted that ORION-4 (n = 16,124), a phase-3 randomised control trial investigating the effects of inclisiran on heart attack and stroke risk over a five year period, will conclude in 2026 providing powered MACE outcomes (NCT03705234).

14.20. ORION-9 (Raal et al. NEJM, 2020;382:1520-30) was a phase-3, double-blind, randomised trial of inclisiran in people with genetically or phenotypically confirmed HeFH (n = 492). Participants received four doses of 284mg inclisiran, on days 1, 90, 270, and 450. 90% of participants were receiving concomitant statin treatment, and 50% of participants were receiving concomitant treatment with ezetimibe. The median baseline LDL-C levels for the treatment and placebo groups were 3.9mmol and 4.0mmol respectively. Median LDL-C levels in the treatment group decreased by 39.7% and increased 8.2% in the placebo group from baseline compared to day 510. Median PCSK-9 levels reduced by 60.7% in the treatment group and increased by 17.7% in the placebo group. The trial reported very few serious adverse events (SAEs), and the majority of AEs were mild-moderate injection site reactions. A post hoc analysis of ORION-9 reported no significant difference between inclisiran and placebo in terms of MACE outcomes (Ray et al. Eur Heart J. 2023;44:129-38).

14.21. ORION-10 (n = 1561) and ORION-11 (n = 1617) (Ray et al. NEJM, 2020;382:1507-19) were randomised, double-blind, placebo-controlled, phase-3 parallel group trials performed in the USA, and Europe and South Africa respectively. The trials enrolled participants with atherosclerotic cardiovascular disease (ASCVD), and ORION-11 also included people with ASCVD risk equivalents. 1.2% of participants in ORION-10 had HeFH, and 1.7% of participants in ORION-11. Participants received four doses of 284mg inclisiran, on days 1, 90, 270, and 450. 89-95% of participants across treatment and placebo groups in both trials were on concomitant statin treatment, and 6-10% were on concomitant ezetimibe treatment. The median baseline LDL-C levels for participants in both trials ranged from 2.7mmol to 2.8mmol in both the treatment and placebo groups. In ORION-10, the median LDL-C levels in the treatment group decreased by 54.8% and increased 3.4% in the placebo group from baseline compared to day 510. In ORION-11, the median LDL-C levels in the treatment group decreased by 51.3% and increased 1.0% in the placebo group from baseline compared to day 510. The Committee considered that no subgroup on the trial population gained more benefit from treatment with inclisiran than the others. The Committee also considered that the reported cardiovascular events were too small to draw conclusions upon.

14.22. The Committee noted the Luo et al. Front Pharmacol. 2023;14:1158274 pooled analysis of ORION-9, ORION-10, ORION-11 trials, investigating the efficacy and safety of inclisiran in stroke or cerebrovascular disease progression in people with ASCVD. The analysis reported that inclisiran provided no benefit for stroke or MACE prevention in

people with ASCVD, but was associated with the reduction of MI, although these results were non-significant.

14.23. The Committee noted the Ray et al. Eur Heart J. 2023;44:129-38 pooled analysis of ORION9, ORION-10, and ORION-11 trials, investigating the efficacy of inclisiran in reducing MACEs, in people with HeFH, ASCVD, or ASCVD risk equivalents. The analysis reported a reduction in MACE events and cardiovascular death associated with the inclisiran, however, these results were considered hypothesis generating due to a lack of powered outcomes from the base trials (i.e., all reported MACE results were exploratory).

14.24. The Committee was noted the Dutta et al. Expert Opin Drug Saf. 2024;23:187-98 pooled analysis of ORION-9, ORION-10, ORION-11 and the phase-2 ORION-1 trials, investigating the efficacy of inclisiran in reducing MACEs and LDL-C in people with hyperlipidemia. The analysis reported a reduction in MACE events and LDL-C associated with inclisiran, however, the analysis of MACE events was considered hypothesis generating due to a lack of powered outcomes from the base trials (i.e., all reported MACE results were exploratory).

14.25. The Committee noted the Deaney et al. Clin Med Insights Cardiol. 2025;19:11795468251337425 observational study of outcomes associated with inclisiran treatment for ASCVD in England (n = 161). At baseline, 60% of participants were being treated with statins, and 24% with ezetimibe. The reported mean LDL-C reductions were statistically significant, and the Committee considered that the LDL-C reduction benefit observed in the ORION trials translated into the observational setting.

14.26. The Committee considered that the three meta-analyses were hypothesis generating and are indicative of benefit beyond LDL-C lowering, however, this cannot be confirmed until the conclusion of the ORION-4 trial in 2026. The Committee considered that the aforementioned evidence for inclisiran in the treatment of HeFH is generalisable and relevant to the New Zealand context.

14.27. The Committee considered that, based on the evidence available to date, inclisiran does not introduce any clinically significant risks compared to currently funded treatments, and that the adverse events (AEs) associated with inclisiran are comparable to currently funded treatments.

*Suitability*

14.28. The Committee noted that inclisiran is supplied as a pre-filled syringe, at a dose of 284mg administered subcutaneously on Day 0, then at three months, and then one dose every six months thereafter. The Committee noted that the evidence found that some people may experience mild-moderate localised site reactions with inclisiran use.

14.29. The Committee considered that the infrequent subcutaneous injection administration of inclisiran may provide a suitability benefit for some individuals, compared to the daily oral administration of statins and ezetimibe. The Committee also noted that inclisiran is to be administered by a health professional.

*Cost and savings*

14.30. The Committee noted the Ostwald et al. Value Health. 2023;26:1353-62 public health cost effectiveness publication using the dynamic Markov model to calculate the societal impact savings accumulated through the use of inclisiran. The publication reported an estimate of 13,8647 cardiovascular events over a period of ten years could be avoided through the use of inclisiran. The resulting value-invest ratio reported was 1.03.

14.31. The Committee noted that the supplier provided uptake estimates of 25%, 35%, 45%, 55% and 60% in years 1-5. The Committee considered that this may be an overestimate of the anticipated uptake in NZ and that uptake is likely to be low until evidence on MACE outcomes is published. The Committee noted that, in the UK, inclisiran was prescribed to only 7% of the population due to physicians erring on the side of caution regarding prescription until long term evidence from the ORION-4 trial is released in 2026 (Connelly, D. Pharmaceutical Times, 2025).

*Funding criteria*

14.32. The Committee considered that the Cardiovascular Advisory Committee would be well placed to advise on the LDL-C thresholds used to identify the population requiring treatment with inclisiran in the Special Authority Criteria.

14.33. The Committee considered the supplier proposed threshold (chosen to target the HeFH subpopulation with the highest risk) for people with HeFH who do not also have ASCVD (i.e., the primary prevention population) of 4.5mmol may be higher than the threshold they would recommend, considering that the median baseline LDL-C levels of the ORION trials participants ranged from 2.7mmol to 4.0mmol. The Committee considered that the application requests that treatment with inclisiran be initiated in the third line setting (after statin and ezetimibe therapies), which reflects the ORION trial populations.

14.34. The Committee noted that internationally, there are a range of LDL-C thresholds used in eligibility criteria for people with HeFH, as listed below:

14.34.1. Australia: 1.8mmol if comorbid with ASCVD and >5.0mmol if not comorbid with ASCVD.

14.34.2. England/Wales: 2.6mmol despite maximum tolerated lipid-lowering therapy

14.34.3. Scotland: ≥5.0mmol/L, for primary prevention of cardiovascular events or, 3.5mmol/L, for secondary prevention of cardiovascular events.

14.34.4. Canada: pre-treatment total cholesterol >7.5 mmol/L or LDL cholesterol >4.9 mmol/L, or ≥ 2 mmol/L despite current therapy.

*Summary for assessment*

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

| | |
|---|---|
| **P**opulation | **Secondary prevention HeFH population**. Adults with a history of heterozygous familial hypercholesterolaemia (HeFH) with atherosclerotic cardiovascular disease (ASCVD), and serum low-density lipoprotein cholesterol (LDL-C) ≥1.4 mmol/L despite maximally tolerated statins (CSANZ, 2021).<br><br>**Primary prevention HeFH population**, Adults with a history of HeFH without ASCVD, and serum low-density lipoprotein cholesterol (LDL-C) ≥4.5 mmol/L despite maximally tolerated statins and ezetimibe. |
| **I**ntervention | Inclisiran, subcutaneous injection administered in an outpatient setting.<br>• 284mg at Day 0, Day 90 and every six months thereafter<br><br>As an adjunctive therapy to other community pharmaceuticals (mainly statins, ezetimibe. |
| **C**omparator(s) (NZ context) | Standard of care pharmacotherapy for the primary or secondary prevention of CVD events |
| **O**utcome(s) | Reduction in LDL-C<br>• LDL-C reductions are associated with a reduction in the risk of major adverse cardiovascular events (CTTC meta-analysis) |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

## 15. Pembrolizumab (Keytruda) for malignant pleural mesothelioma (MPM)

### Application

15.1. The Committee reviewed the application for pembrolizumab with pemetrexed the treatment of malignant pleural mesothelioma.

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

### Recommendation

15.3. The Committee **recommended** that the application for funding pembrolizumab with pemetrexed and platinum-based chemotherapy for people with all subtypes of malignant pleural mesothelioma be **declined**.

15.4. The Committee **recommended** that pembrolizumab with pemetrexed and platinum-based chemotherapy be funded with a **medium priority** for non-epithelioid subtypes malignant pleural mesothelioma, subject to the following Special Authority criteria:

**Initial application** – pembrolizumab (malignant pleural mesothelioma non-epithelioid subtypes only) Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Person has advanced malignant pleural mesothelioma; and
2. Disease is categorised as a non-epithelioid subtype; and

3. Person has ECOG performance status 0-2; and
4. Person has not received any previous treatment for their malignant pleural mesothelioma; and
5. Pembrolizumab is to be used in combination with chemotherapy; and
6. Pembrolizumab to be administered at a maximum dose of 200mg every 3 weeks (or equivalent).

**Renewal Application –** Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria: All of the following:

1. Either:
   1.1. Person's disease has had a complete response to treatment; or
   1.2. Person's disease has had a partial response to treatment; or
   1.3. Person has stable disease;
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. Pembrolizumab to be administered at a maximum dose of 200mg every 3 weeks (or equivalent); and
4. Maximum treatment period of 24 months (cumulative total of initial plus renewed treatments).

15.6. When making these recommendations the Committee considered

15.6.1. The high health needs of those with malignant pleural mesothelioma, which were noted to be greater for those with non-epithelioid histology.

15.6.2. The meaningful benefit in overall survival associated with pembrolizumab with pemetrexed and platinum-based chemotherapy for those with non-epithelioid histology.

15.6.3. The available evidence suggested only a marginal health benefit when assessed across subtypes, but particularly in those with epithelioid histology.

15.7. The Committee acknowledged that its recommendation to decline funding pembrolizumab (with chemotherapy) for people with all subtypes of malignant pleural mesothelioma may not align with previous recommendations for other treatments for this patient population. Members noted the differences in evidence and suggested it would be appropriate to discuss this further at a future meeting.

## Discussion

*Māori impact*

15.8. The Committee discussed the impact of funding pembrolizumab with pemetrexed on Māori health outcomes. Members noted that malignant pleural mesothelioma (MPM) is not among the five Māori health areas of focus | Hauora Arotahi.

*Populations with high health needs*

15.9. The Committee discussed the health needs among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee noted that these populations were not represented in the pivotal clinical trial, and no specific evidence was available to inform outcomes for these groups. Members considered broader patterns of cancer-related inequities—such as differential access to care, timeliness of diagnosis, survivorship outcomes, and historical occupational exposures—but were not aware of any evidence indicating disparities in the prevalence or prognosis of MPM specific to these populations. The Committee acknowledged that the absence of evidence does not preclude the possibility that such inequities may exist.

15.10. The Committee considered that lower socioeconomic groups may be disproportionately affected due to cost barriers to asbestos remediation, and that Māori and Pacific peoples may carry additional risk factors such as higher smoking rates.

*Background*

15.11. The Committee noted having previously reviewed a funding application for the 1st line use of nivolumab with ipilimumab for the treatment of MPM in February 2025 (link to meeting record). The Committee noted its recommendation to fund the regimen for all histological subtypes of MPM with a low priority, and non-epithelioid subtypes with a medium priority. The Committee acknowledged that the populations targeted in their past review to be the same as indicated for this application.

15.12. The Committee noted that nivolumab with ipilimumab or pembrolizumab with pemetrexed and platinum-based chemotherapy have been accessed through the Accident Compensation Corporation (ACC) for the treatment of MPM.

*Health need*

15.13. The Committee considered the health needs of those living with MPM to be comprehensively documented in the meeting record from the Committee's prior review of nivolumab with ipilimumab February 2025 (link to meeting record). Specifically, members agreed and reiterated that

15.13.1. MPM is an aggressive, incurable condition often diagnosed at an advanced stage. The high symptom burden and poor prognosis across all subtypes establish the high health need for people living with MPM.

15.13.2. People with nonepithelioid histology (sarcomatoid, biphasic) have worse prognosis and shorter survival than those with epithelioid histology and therefore have relatively higher health needs.

15.13.3. Exposure to asbestos is a major risk factor for MPM, commonly arising through occupational settings.

*Health benefit*

15.14. The Committee noted KEYNOTE-483 as key evidence (Chu et al. Lancet 2023;402: 2295-306). KEYNOTE-483 was an international, phase III, randomised controlled trial which investigated pemetrexed + platinum-based chemotherapy (P/PBC, n=218) versus those who received pembrolizumab in addition to P/PBC (n=222) in people with MPM with no prior treatment. The primary endpoint was overall survival (OS). Members noted that of the 440 participants enrolled, 77% of trial participants had epithelioid histology, 76% were male, and the median age was 71 years which was reflective of the population that are diagnosed with mesothelioma. The median follow-up duration was 16 months. At the data cut-off, 342 participants had died.

15.14.1. The committee noted that in the full study population, there was a modest gain in median OS for those received pembrolizumab (17.28 months, 95%CI 14.36-21.29) compared to those who did not (16.13 months, 95%CI 13.08-18.17). The estimated treatment effect was statistically significant (HR: 0.79, 95%CI 0.64-0.98; p=0.0324).

15.14.2. The Committee considered that the benefit appeared greater in non-epithelioid subtypes, although members noted the subgroup analysis was not preplanned. Members noted that participants with epithelioid histology appeared to derive marginal or no benefit in median overall survival (OS) from the addition of pembrolizumab, with a median OS of 19.8 months (95% CI: 16.0–22.2) compared to 18.2 months (95% CI: 16.0–20.4) in the P/PBC only arm (HR: 0.89; 95% CI: 0.70–1.13). In contrast, participants with non-epithelioid histology experienced a more pronounced benefit (HR: 0.57; 95% CI: 0.36–0.89), with a median OS of 12.3 months (95% CI: 8.67–21.20) compared to 8.21 months (95% CI: 5.85–10.80) in the control arm. The Committee noted the shorter OS observed in the

non-epithelioid subgroup relative to the epithelioid subgroup and considered the non-preplanned nature of the histological subgroup analysis to be a limitation on the validity of these findings.

15.14.3. The Committee discussed findings related to treatment toxicity and noted that 98% of participants who received pembrolizumab and P/PBC experienced at least one adverse event, and 27% of participant experienced of an adverse event of grade 3 or 4 severity. In comparison, 95% of those who received P/PBC-only experienced at least one adverse event, and 15% experienced an adverse event of grade 3 or 4 severity. The Committee acknowledged that the toxicity of a checkpoint inhibitor combined with chemotherapy is commonly managed across a variety of disease settings in oncology, and noted the complex care and significant resource that can be required.

15.14.4. The Committee discussed the quality of the evidence provided by KEYNOTE-483 and considered the lack of a preplanned histological subgroup analysis to be a limitation of the subgroup findings. The Committee did not identify any significant concerns with the overall quality or generalisability of the evidence.

15.14.5. The committee considered that even small gains in OS are meaningful to the affected individual and their whānau.

15.15. The Committee reviewed the health benefits of nivolumab and ipilimumab regimen as evidenced in CHECKMATE-743 (Peters et al. Ann Oncol. 2022;33:488-99). The Committee noted that compared to Keynote 483, CHECKMATE-743 features a published analysis on matured data set (median follow up: 43.1 months), and the study included a preplanned analysis by histological subtype. Kaplan-Meier survival analyses for both the overall study population and histological subgroups were reviewed. The observed trends were consistent with those reported in KEYNOTE-483, with a greater treatment benefit evident in the non-epithelioid subgroup (OS HR 0.48; 95%CI: 0.34-0.69) compared to the overall population (OS HR 0.73; 95%CI: 0.61-0.87)

15.15.1. The Committee noted the similarities between CHECKMATE-743 and KEYNOTE-483 and considered that indirect comparison of the trial results was reasonable, although such observations were regarded as hypothesis-generating rather than confirmatory. Members noted that the nivolumab plus ipilimumab regimen appeared to have a more favourable overall survival hazard ratio compared with the pembrolizumab (with chemotherapy) regimen. The Committee considered that the overall survival dataset from CHECKMATE-743 was more mature compared to data available from KEYNOTE-483. The Committee considered there to be uncertainty regarding whether the reported difference in OS hazard ratio is clinically meaningful.

15.15.2. The Committee considered that, in KEYNOTE-483, the pembrolizumab plus P/PBC regimen appeared to be generally less well tolerated than the nivolumab plus ipilimumab regimen in CHECKMATE-743, although member reiterated the low confidence associated with this indirect comparison. Overall, the risk profiles of both treatments were considered to differ slightly but remain generally manageable. Members noted that both regimens may require complex and prolonged management of immune-related adverse events.

15.16. The Committee reviewed the findings of Messori et al. Cancers. 2025;17:503, an independent indirect treatment comparison which included the findings of CHECKMATE-743 and KEYNOTE-483. Members noted that both the Pembrolizumab with P/PBC and the Nivolumab with Ipilimumab regimens were found to have a significant incremental benefit in OS compared to P/PBC alone.

15.17. The Committee noted that, according to the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS), which scores treatments in a non-curative setting from 1 (lowest benefit) to 5 (highest benefit), pembrolizumab with P/PBC scored 1 (ESMO-MCBS scorecard), while nivolumab with ipilimumab scored 3 (ESMO-MCBS scorecard). The Committee also noted that this scoring difference was influenced

by the availability of quality-of-life data in CHECKMATE-743 trial, whereas KEYNOTE-483 was scored without these outcomes available.

*Suitability*

15.18. The Committee considered that, compared with pembrolizumab plus pemetrexed and platinum-based chemotherapy, the toxicity of nivolumab plus ipilimumab may better managed in physically unwell or older patients, offering a slight suitability advantage for these individuals. Members considered this was based on anecdotal evidence due to a lack of robust comparative data.

*Cost and savings*

15.19. The Committee noted that pembrolizumab is added to chemotherapy, whereas nivolumab with ipilimumab replaces chemotherapy. The Committee considered there may be more resource involved in the administration of the pembrolizumab regimen, but requested Pharmac review this while assessing both proposals.

15.20. The Committee considered that the management of immunotherapy toxicity requires significant resource and time within treatment centers. Members considered this requirement would not differ materially were either nivolumab + ipilimumab or the pembrolizumab regimen be funded.

15.21. The Committee Considered that although there were some differences in health benefit reported between the investigational arms of CHECKPOINT-783 and KEYNOTE-483, the treatment benefits were sufficiently similar that it is reasonable to run a competitive procurement process to obtain a single treatment for people with non-epithelioid subtypes malignant pleural mesothelioma.

*Funding criteria*

15.22. The Committee considered that if funded, pembrolizumab should be restricted to non-epithelioid subtypes, consistent with the subgroup showing greatest benefit.

*Summary for assessment*

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

| | |
|---|---|
| **P**opulation | Previously untreated individuals with advanced or metastatic non-epithelioid malignant pleural mesothelioma |
| **I**ntervention | Pembrolizumab<br>• First six cycles: Pembrolizumab (200 mg) with pemetrexed (500mg/m$^2$) + cisplatin (75 mg/m$^2$) OR carboplatin (AUC 5-6 mg/mL/min) every 3 weeks<br>• Subsequent cycles: Pembrolizumab (200 mg) every 3 weeks for up to 2 years or until disease progression, whichever occurs first. |
| **C**omparator(s) (NZ context) | Pemetrexed (500 mg/m$^2$) + cisplatin (75 mg/m$^2$) or carboplatin (AUC 5-6 mg/mL/min) every 3 weeks for 6 cycles |
| **O**utcome(s) | Overall survival (OS), Progression-free survival (PFS), Objective Response Rate (ORR), and safety |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |