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 17 August & 18 August 2023

1. Present:

PTAC members:
Jane Thomas (Chair)
Rhiannon Braund (Deputy Chair)
Brian Anderson
Bruce King
Elizabeth Dennett
John Mottershead
Liza Lack
Matthew Dawes
Matthew Strother
Paul Vroegop
Simon Wynn Thomas
Stephen Munn

PTAC members in attendance for parts of the meeting:
Lisa Stamp

Apologies:
Alan Fraser
Robyn Manuel

Guests:
Scott Arrol (Motor Neurone Disease New Zealand)
Laura Huet (Motor Neurone Disease New Zealand)
Jo Kelly (Motor Neurone Disease New Zealand)

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

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

Pharmaceutical and Indication	Recommendation
9.5. Food thickeners	
10.4. Empagliflozin for the treatment of diabetes mellitus type 2 (T2DM), removal of HbA1c threshold	**High priority**
10.6. GLP-1 agonists for the treatment of diabetes mellitus type 2 (T2DM) GLP-1 agonists, removal of HbA1c threshold	**Declined**
11.4. Empagliflozin, chronic kidney disease, non-diabetic	**High priority**
12.4. Tocilizumab for giant cell arteritis	**Medium priority**
13.4. Infliximab, subcutaneous infliximab for the treatment of all current indications as intravenous infliximab	**High priority**
14.4. Ofatumumab for relapsing remitting multiple sclerosis	**Cost-neutral**

4. Records of PTAC meetings held on 16 & 17 February and 18 May & 19 May 2023

4.1. The Committee reviewed the records of the PTAC meetings held on16 February & 17 February and 18 May & 19 May 2023

4.2. The Committee accepted the records.

5. Specialist Advisory Committee Records

PTAC and Specialist Advisory Committees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives

2023-03-02 Immunisation Advisory Committee Meeting record

5.1. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee meeting held on 2 March 2023.

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

2023-03-28 Rheumatology Advisory Committee record

5.3. The Committee (PTAC) reviewed the record of the Rheumatology Advisory Committee meeting held on 28 March 2023.

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

2022-11-09 Haematology Advisory Committee meeting record

5.5. The Committee (PTAC) reviewed the record of the Haematology Advisory Committee the meeting held 9 November 2022.

5.6. The Committee noted that the horizon scanning section of the meeting had identified several treatments currently in the pre-commercialisation stage of development that would likely have a significant impact on future treatment paradigms in haematology.

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

2023-01-27 CTAC Ad Hoc meeting record

5.8. PTAC reviewed the record of the Cancer Treatments Advisory Committee Ad Hoc meeting held on 27 January 2023.

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

2022/23 Combined COVID-19 Treatments Advisory Group Records

5.10. PTAC reviewed the records of the COVID-19 Treatments Advisory Group meetings held between 28 February 2022 and 14 February 2023.

5.11. PTAC noted the records.

5.12. PTAC queried the ongoing need for COVID-19 specific treatments and the COVID-19 Treatments Advisory Group. PTAC noted that Pharmac is working to align COVID-19 treatments with its usual activities for the funding of pharmaceuticals, including incorporating COVID-19 treatments within the Anti-infectives Therapeutic Group in the longer term.

2023-04-20 Diabetes Technology RFP - Record from the April 2023 Diabetes Advisory Committee

5.13. The Committee (PTAC) reviewed the record of the Diabetes Advisory Committee the meeting held on 20 April 2023.

5.14. The Committee noted that the main focus of the meeting was to seek advice on the CGM and insulin pump procurement activity, which was released on 11 July 2023.

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

6. Correspondence & Matters Arising

Food Thickeners

Application

6.1. The Committee considered the funding of food thickeners following Pharmac's February 2023 consultation to phase out funding of food thickeners in the community.

6.2. The Committee viewed a presentation from Motor Neurone Disease NZ, highlighting the health need of people with motor neurone disease in New Zealand and the benefit offered by food thickeners for people with motor neurone disease living in the community.

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

Recommendation

6.4. The Committee **recommended** that access to funded food thickeners be retained in the community for people with motor neurone disease with a swallowing disorder.

6.5. In making this recommendation, the Committee:

- Considered the health need of people with motor neurone disease with a swallowing disorder and their caregivers/family/whānau, and the benefits and risks of food thickeners versus other available treatments and timing of treatments (including earlier insertion of PEG or similar surgical interventions for progressive dysphagia).

- Noted that food thickeners have been available and funded in New Zealand for the management of dysphagia for people with motor neurone disease in the community for a number of years, and that their use is an established and long-standing aspect of clinical practice, which is supported by New Zealand and international clinical guidelines.

- Noted there have been no randomised clinical trials undertaken to evaluate the benefit of food thickeners specifically for people with motor neurone disease or other groups of people with persistent and progressive swallowing disorders.

- Noted that specific clinical trials have been undertaken in populations with dysphagia due to causes, such as stroke, that may stabilise or improve over time and considered that as these trials suggest there is no benefit associated with the use of food thickeners for these groups, widened access to these population groups cannot be supported at this time.

- Considered that people with persistent and progressive swallowing disorders would have a similar health need to people with motor neurone disease who have a swallowing disorder with respect to their swallowing and its health impact.

- Reiterated its concerns around the risk of harm from the longer-term use of food thickeners in people without progressive dysphagia.

6.6. The Committee considered that further work needed to be undertaken by Pharmac to better define the groups of people with persistent and progressive swallowing disorders, who would be considered to have an equivalent health need to the currently funded group with motor neurone disease.

6.7. The Committee considered it was likely this would include people with persistent and progressive swallowing disorders that lead to significant weight loss where surgical interventions such as a percutaneous endoscopic gastrostomy (PEG) are indicated to meet nutritional and/or hydration requirements, or people with similar presentations where PEG insertion is not possible.

Discussion

Māori impact

6.8. The Committee discussed the impact of funding food thickeners in the community for people with persistent and progressive swallowing disorders, including motor neurone disease on Māori health areas of focus and Māori health outcomes. The Committee noted that persistent and progressive swallowing disorders were not specifically identified as a Māori health area of focus and were not expected to impact Māori at higher rates than other population groups in New Zealand, although information regarding this was not readily available due to the small numbers of people expected.

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

6.9. The Committee noted there was a lack of evidence to assess the impact of funding food thickeners in the community for people with persistent and progressive swallowing disorders among Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system.

Background

6.10. The Committee noted that in February 2023 Pharmac had released a public consultation on a proposal to phase out the funding of food thickeners in the community. The Committee noted that the vast majority of the responses received did not support Pharmac's proposal and requested that access to food thickeners in the community be retained and widened to include people with dysphagia due to causes other than motor neurone disease.

6.11. The Committee noted the responses to the consultation. The Committee appreciated and valued the information shared by Motor Neurone Disease NZ regarding the health need and lived experience of people with motor neurone disease in New Zealand and the use of food thickeners to help manage their condition.

6.12. The Committee noted the extensive history of clinical advice from PTAC and Pharmac's Specialist Advisory Committees (previously PTAC Subcommittees) for the use of food thickeners in the community. The Committee noted that PTAC had most recently considered the funding of food thickeners in the community in 2021 following the release of a Request For Information by Pharmac.

6.13. The Committee noted that two brands of food thickeners were currently funded for use in hospital and in the community for people with dysphagia (swallowing difficulties), with community funding restricted to people with motor neurone disease with a swallowing disorder. The Committee noted that this restricted community funding was inconsistent with clinical practice, as dysphagia can occur in conditions other than motor neurone disease.

6.14. The Committee noted that the rationale for funding food thickeners in the community for people with motor neurone disease with swallowing disorder (and not funding for other causes of dysphagia/swallowing disorder) is not apparent and appears to have arisen shortly after the establishment of Pharmac.

6.15. The Committee noted that the inconsistent funding of food thickeners in the community had resulted in a complaint to the Human Rights Commission (HRC) alleging discrimination on the basis of disability. This complaint was on the grounds that food thickeners in the community are currently funded for one group of people with a particular underlying condition, and not for people with different underlying conditions, even though both groups were said to require the product to address the same health need– namely dysphagia.

6.16. The Committee noted that in 2021 PTAC had considered a range of information regarding the funding of food thickeners in the community, and that the purpose of the present discussion was to consider any new information not considered already in 2021, and to consider the responses to the February 2023 consultation.

6.17. The Committee noted that in 2021 it had also confirmed its previous recommendation that the community funding of food thickeners be delisted from the Pharmaceutical Schedule as there was insufficient evidence that food thickeners would be expected to address the unmet needs and provide clinically meaningful benefits for people with dysphagia. Additionally, the Committee had noted there is some evidence of a risk of

harm from use of food thickeners in dysphagia, and it would be difficult to define a specific population that may benefit from food thickeners.

Health need

6.18. The Committee noted that there were a large number of conditions that could result in dysphagia. The Committee considered that people with dysphagia could be split into two groups. The first group is people with dysphagia that stabilises or improves over time. The second group experiences persistent and progressive dysphagia that worsens with time, frequently caused by underlying diseases causing lifespans that are time-limited, and leads to significant weight loss and/or dehydration, and the recommendation of surgical interventions such as a percutaneous endoscopic gastrostomy (PEG) to meet nutritional/hydration requirements. The Committee considered that the latter group would have a higher health need than other people with dysphagia. The Committee considered that this group would include people with bulbar and pseudo bulbar palsy, including but not limited to, people with motor neurone disease, people with advanced Parkinson's disease, people with advanced multiple sclerosis, and people with Huntington's disease.

6.19. The Committee considered that the number of people in this group would be small and the majority would be included in the currently eligible group of people with motor neurone disease.

6.20. The Committee considered further work would need to be undertaken by Pharmac staff, including engagement with relevant specialists, to clearly define the group of people with persistent and progressive dysphagia in New Zealand, and to determine whether any widening of access criteria is required to include all people in this group.,.

6.21. The Committee noted that coughing and choking while eating and drinking is uncomfortable and distressing for people with persistent and progressive dysphagia, their whānau, and caregivers.

6.22. The Committee noted that the people with persistent and progressive dysphagia with the highest health need would require feeding via a PEG or other similar surgically placed interventions as their dysphagia worsened. The Committee noted that there would be a subset of this group who are unable to receive a PEG, or similar intervention, due to deteriorating respiratory function and significant perioperative risk. .

6.23. The Committee considered there was currently a high unmet need for people with persistent and progressive dysphagia, and noted there was often no cure for the underlying cause of their dysphagia and they typically have very short life expectancies. The Committee considered that due to this high unmet health need, even a small improvement in quality of life could have a pressing and meaningful impact.

6.24. Members discussed whether, the threshold of evidence for ongoing funding in the community of any pharmaceutical might differ from the evidentiary threshold for widening of access of any pharmaceutical to new population groups or funding a novel treatment. Members considered the latter might be expected to better demonstrate evidence of benefit.

6.25. Members noted that people with motor neurone disease and the clinicians may consider that any removal of funding of food thickeners in the community would

increase their health need.

6.26. The Committee noted information from Motor Neurone Disease NZ that due to the rapidly progressive nature of their disease, people with motor neurone disease in New Zealand typically receive food thickeners for a period of 6 months, with a small number of people receiving food thickeners for up to 12 months.

6.27. The Committee noted that in addition to food thickeners other options are available to help people manage their dysphagia such as using the chin down technique when swallowing, pacing when eating and drinking, posture, and pureed food, however these techniques are unlikely to fully resolve a person's dysphagia.

6.28. The Committee noted that people with dysphagia would typically be cared for by a multidisciplinary team, including Speech Language Therapists who advise on appropriate options including the use of food thickeners.

6.29. The Committee noted that video-fluoroscopic swallowing studies (VFSS) are often requested by Speech Language Therapists to establish a diagnosis and demonstrate aspiration. Liquids of different thickness can be evaluated via VSS to determine whether thickening reduces aspiration.

6.30. Members noted that the thickening of fluids and foods to reduce aspiration would not reduce aspiration occurring outside of eating and drinking.

Health Benefit

6.31. The Committee recalled the evidence it had reviewed as part of its February 2021 consideration of the community funding of food thickeners.

6.32. The Committee considered research that had become available since its February 2021 review of food thickeners, as well as information it had not considered in 2021, including the following:

6.32.1. Steele et al. Breathe 2021;17:210003
This review of the evidence for thickened fluids in the management of dysphagia concluded that there is no evidence to support the clinical benefits of thickened fluids in the treatment of dysphagia. In addition, there was some evidence that thickened fluids are a poorly tolerated intervention associated with lower health related quality of life and increased risks of malnutrition and dehydration.

6.32.2. Kaneoka et al. Clin Rehabil 2017;31:1116-25
A systematic review and meta-analysis of published or unpublished randomised controlled trials and prospective non-randomised trials comparing the incidence of pneumonia with intake of thin liquids plus safety strategies vs thickened liquids in adult patients who have previously aspirated on thin liquids. This concluded that amongst patients with a low risk of pneumonia there was no significant difference in the risk of pneumonia in patients who took thin liquids with safety strategies compared with those who took thickened liquids only (odds ratio (OR) 0.82, 95% CI 0.05-13.42, p = 0.89).

6.32.3. Ahn et al. Medicine (Baltimore). 2022;101(38)
This observational pilot study investigated the status of thickener use in twenty dysphagia patients with brain lesions and then measured the incidence of adverse events based on fluid viscosity. Forty percent of the cases did not successfully formulate their thickener to correct viscosity, as trained.

6.32.4. Onesti et al. Front Neurol. 2017; 8:94
A retrospective study conducted over a two year period which aimed to investigate the clinical features associated with deteriorated swallow in one hundred forty-five people with amyotrophic lateral sclerosis (ALS) with spinal and bulbar onset and describe the modification of diet and liquid intake. The study concluded that the frequency of use of normal and semi-solid diets decreased over time, while that of pureed diets and PEG prescription increased. Forty-four percent of dysphagic patients refused thickeners or PEG.

6.33. The Committee noted a systematic review of international clinical guidelines on use of thickened fluids for dysphagia post stroke, which the Committee had reviewed in May 2021, which noted 13 clinical guidelines were available and, despite the lack of clinical evidence available the consensus statements were that thickened fluids were recommended (McCurtin et al. J Eval Clin Pract. 2020;26:1744-60)

6.34. The Committee noted that there was no new primary research or clinical trial evidence or food thickeners in dysphagia, including dysphagia in motor neurone disease, and that newly published systematic reviews included previously reviewed primary evidence. The Committee considered that there was no new evidence to support the benefits from food thickeners.

6.35. Overall, the Committee considered that the evidence available did not support the use of food thickeners for the management of dysphagia.

6.36. The Committee noted references to the use of food thickeners were included in the New Zealand Best Practice Recommendations for people with Motor Neurone Disease, which were produced by Motor Neurone Disease New Zealand.

6.37. The Committee noted that there were a very limited number of high-quality trials that had been undertaken to evaluate the benefit associated with food thickeners and considered that none of these trials reported any benefit associated with the use of food thickeners in the management of dysphagia.

6.37.1. The Committee noted that these trials had been undertaken in populations with dysphagia from a range of causes and severities, and none of them included people with motor neurone disease or other similar groups with persistent and progressive dysphagia.

6.37.2. In addition, the Committee considered the endpoints investigated in the studies, such as a reduction in aspiration pneumonia and overall improvements in quality of life, may miss a small group of people with dysphagia who are receiving some benefit from the use of food thickeners.

6.38. The Committee noted that the use of food thickeners in the management of dysphagia was an established and long-standing aspect of clinical practice in New Zealand. The Committee noted that any recommendation to remove funded food thickeners from the community would be contrary to international guidelines for the management of dysphagia, noting again however the apparent paucity of clinical evidence supporting guidelines' recommendations (McCurtin et al. 2020).

6.39. The Committee noted that there was evidence that the inappropriate use of food thickeners could result in harm, including malnourishment or dehydration. The Committee also noted that the ongoing availability of food thickeners in the community could possibly lead to people missing out on the window of opportunity to receive a PEG insertion, resulting in poorer health outcomes. However, the

Committee considered any incidence of this would be limited and members were not aware of this arising in clinical practice.

Suitability

6.40. The Committee noted feedback received in response to Pharmac's February 2023 consultation, that the two brands of food thickener funded by Pharmac were not preferred in the management of dysphagia as they are starch based thickeners, which can result in a grainy or lumpy texture, compared to thickeners made from other agents such as xanthan gum or guar gum.

6.41. The Committee noted that the thickeners that are currently funded by Pharmac were supplied as a powder and needed to be mixed by the person with dysphagia or their carers, which could make reliably achieving a desired viscosity challenging.

6.42. The Committee noted that some people would not be able to afford other types of preferred thickener and these people were likely to be accessing the currently funded products.

6.43. The Committee noted that premixed, thickened fluids were available, which could avoid the issues with texture and viscosity associated with the currently available thickeners. The Committee was unsure if premixed, thickened fluids would be preferred by people with dysphagia, as they could not be mixed with food or beverages the person already enjoyed.

6.44. Members noted that many people with dysphagia who were recommended to use a thickener did not like using them and chose to continue consuming unthickened food and fluids.

6.45. Members noted that the ongoing availability of food thickeners in the community could allow for a more individualised approach to be taken to the management of dysphagia than if they were not available.

Costs and savings

6.46. The Committee noted that, based on current pricing, the per unit cost associated with funded food thickeners was relatively low and would be estimated to cost $364 per person per year assuming 26 cans were used each year.

6.47. The Committee noted that if the access was widened to include all people with dysphagia, the cost to the Combined Pharmaceutical Budget could be substantial.

General

6.48. The Committee did not consider it would be appropriate to include an assessment by a Speech Language Therapist in any Special Authority criteria for access to food thickeners in the community, because access to Speech Language Therapists was unlikely to be equitable across the country and could present a barrier to access for some people. In addition, it was noted that even if people were able to access a Speech Language Therapist, access to video-fluoroscopic swallowing studies was unlikely to be available to all people in New Zealand.

6.49. The Committee noted that there was evidence to support the use of PEG feeding in the management of dysphagia, and positive health outcomes associated with this. The Committee considered it would be supportive of greater access to PEG

insertions for people with dysphagia. It was noted that this would be dependent on the availability of relevant surgical time and resource which may not be available across regions.

6.50. The Committee reiterated its concerns around the risk of harm from the longer-term use of food thickeners in people without progressive disease.

Summary for assessment

6.51. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for food thickeners if they are to continue to be funded in New Zealand for people with persistent and progressive swallowing disorders, including motor neurone disease. 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. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with persistent and progressive swallowing disorders including motor neurone disease, which result in substantial weight loss and dehydration and the recommendation of surgical interventions such as a percutaneous endoscopic gastrostomy (PEG) to meet nutritional requirements, or people with similar presentations where PEG insertion is not possible.
Intervention	Food thickeners
Comparator(s)	Best supportive care, PEG insertion or other similar surgical interventions
Outcome(s)	-Improved quality of life -Stabilised weight or reduced weight loss.

Table definitions:

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

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

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

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

Polypill

Application

6.52. The Committee reviewed the application for aspirin, atorvastatin and ramipril combination pill for the secondary prevention of cardiovascular events following receipt of a letter addressed to the Pharmac Board Chair from a population health academic.

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

Recommendation

6.54. The Committee **recommended** that Polypill be funded only if **cost-neutral** to the component pharmaceuticals.

6.55. In making this recommendation, the Committee considered:

- the health need of people with cardiovascular disease (CVD) and their caregivers/family/whānau, the particular needs of Māori and other populations experiencing inequitable access to cardiovascular medicines.
- that the recent removal of the community prescription co-payment meant there was no financial benefit to the patient in a reduced frequency of scripts.
- that the available evidence did not clearly demonstrate a clinical advantage for the polypill relative to usual care using separate therapeutic products.
- that although the available evidence suggested an improvement in the measure of medication adherence for individuals receiving the polypill, this did not translate into meaningful improvements in final clinical endpoints relative to the comparator.

Discussion

Māori impact

6.56. The Committee discussed the impact of cardiovascular disease on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori experienced worse cardiovascular outcomes compared to non-Māori. The Committee noted that Māori had a greater one-year risk of death after myocardial infarction compared to people of European/other ethnicity (adjusted hazard ratio [HR] 1.77; 95% CI, 1.44 to 2.19) (Mazengarb et al. N Z Med J. 2020;133:1521).

6.57. The Committee understood there is a well-documented body of evidence that CVD is a significant burden for Māori and that Māori are disproportionately exposed to risk factors for CVD such as type 2 diabetes, obesity and tobacco smoking. The Committee also noted evidence that Māori experienced inequitable access to cardiovascular assessment in primary care (Gu et al. J Prim Care. 2014;6: 286-94).

6.58. The Committee noted that for a range of reasons, adherence to statin therapy is lower, and discontinuation rates are higher, in Māori compared to non-Māori, non-Pacific people (Sigglekow et al. PLoS One. 2020;15:e0242424; Kerr et al. J Prim Health Care. 2016;8:238-49; Muniandy et al. N Z Med J. 2021;134:31-45).

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

6.59. The Committee discussed the impact of cardiovascular disease on Pacific peoples' health outcomes. The Committee noted that Pacific people experienced worse cardiovascular outcomes compared to non-Māori non-Pacific people, with twice the one-year risk of death after myocardial infarction (adjusted HR 2.98, 95% CI 2.34 to 3.81) (Mazengarb et al. 2020). The Committee considered Pacific people disproportionately exposed to type 2 diabetes, obesity, and tobacco smoking, and likely experienced inequitable access to cardiovascular assessment in primary care. The Committee noted lower statin adherence and higher statin discontinuation rates in Pacific peoples compared to non-Māori non-Pacific people (Sigglekow et al. 2020; Kerr et al. 2016; Muniandy et al. 2021).

6.60. The Committee considered there was a lack of evidence to assess the impact of cardiovascular disease among disabled people, tāngata whaikaha Māori and people who have been underserved by the health system. The Committee considered that groups in the community who experienced inequitable access to primary care were less likely to appropriate care for cardiovascular disease.

Background

6.61. The Committee acknowledged receipt of a letter addressed to the Pharmac Board Chair from a population health academic (the respondent) expressing concerns that there was a mismatch between the Pharmac Te Whaioranga strategy and the nature of equity considerations by the Committee. The respondent specifically referenced the PTAC meeting held in February 2022 where additional evidence for the polypill application was discussed. The respondent suggested that a polypill-based approach should be implemented as an additional strategy to support a reduction in treatment inequity. The respondent also considered that specific outcome trials are not required to support the introduction of a polypill option for the secondary prevention of CVD in New Zealand.

Health need

6.62. The Committee noted that the secondary prevention of cardiovascular disease (CVD) may involve the use of multiple medications to control modifiable risk factors, as well as dietary and exercise-related interventions, to reduce the risk of cardiovascular event recurrence. The Committee considered that regular access to primary care, cardiovascular risk assessment, and cardiovascular medications were important components of secondary prevention.

6.63. The Committee noted that Māori and Pacific peoples had an age-standardised dispensing rate ratio for statins of 1.4 times compared to non-Māori, non-Pacific people. The Committee noted however that Māori and Pacific peoples experience a disease burden attributable to CVD, as measured by disability-adjusted life-years, that was 3.3 times as high compared to non-Māori, non-Pacific peoples.

6.64. The Committee considered that the listing of a polypill solution may not impact on access equity as often the real barrier for patients is the ability to access adequate primary care for long-term follow-up following a cardiovascular event. The use of a polypill may also result in patients receiving less than optimal medication dosing as the important titration process may be compromised.

Health benefit

6.65. The Committee considered a new and recent randomised controlled trial that assessed the efficacy of a polypill-based strategy, compared with usual care, for reducing the risk of a composite cardiovascular outcome (comprised of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or urgent revascularisation) (Castellano et al; SECURE Investigators. N Engl J Med. 2022;387:967-7). The intervention group received a polypill that contained ramipril/atorvastatin/aspirin in a fixed dose while the other group received usual care using the separate component medications. The Committee noted that while the study reported superior adherence for the polypill group (74.1% versus 63.2% at 24 months [HR 1.17; 95% CI, 1.10 to 1.25]) and lower cardiovascular related mortality (8.2% versus 11.7% [HR 0.67; 95% CI 0.47 to 0.97]), the risk of all-cause mortality was not significantly different between the two groups (HR 0.97; 95% CI 0.75 to 1.25). The Committee noted that the proportion of participants on a lower statin dose

was higher in the usual care group than in the polypill group.

6.66. The Committee noted that the respondent had included some additional references in their letter that had not been previously considered. The Committee considered however that these references did not add significantly to the body of evidence previously evaluated, as they were either review articles or meta-analyses.

Suitability

6.67. The Committee noted that the polypill has clinical suitability over usual care as it reduces the pill burden in management of CVD. It was noted however that in the Castellano et al (2022) study, the average pill burden per day for the polypill group was three compared to five for the usual care group.

6.68. The Committee was made aware of evidence in New Zealand settings that the actual pill burden in terms of number of tablets/capsules was less a barrier to adherence than the need to adhere to multiple treatment times during the day. The Committee considered that the polypill would have negligible impact on the latter.

6.69. The Committee considered that the 40 mg dose of atorvastatin in the polypill would likely be insufficient for most individuals. The Committee understood that many patients seen in primary care would require higher doses of 80 mg a day to achieve an adequate lowering of LDL cholesterol.

6.70. The Committee considered that some individuals receiving a polypill would require an anti-platelet therapy in addition to aspirin, and this would represent another tablet or capsule in addition to the polypill for an individual to take.

Cost and savings

6.71. The Committee noted that at the current price, the cost of the polypill was significantly higher than the separate component medications. The Committee considered that there was a considerable opportunity cost associated with funding medications for which there was a lack of evidence to support a clinically meaningful health benefit.

6.72. The Committee noted that with the recent removal of community prescription co-payments made access to currently funded cardiovascular medicines less costly to individuals. The Committee noted that previously, the co-payment was a cost barrier to access to community pharmaceuticals.

7. Empagliflozin, diabetes mellitus type 2, remove the HbA1c threshold

Application

7.1. The Committee reviewed the application for empagliflozin and GLP-1 agonists for the treatment of diabetes mellitus type 2 (T2DM).

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

Recommendation

- Empagliflozin

7.3. The Committee **recommended** access to empagliflozin be amended to remove the HbA1c threshold with a **high priority** subject to the following Special Authority criteria (removal crossed out, additions in **bold**):

> Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> 1. Patient has previously received an initial approval for a GLP-1 agonist; or
> All of the following:
> 2. Patient has type 2 diabetes; and
> 3. Any of the following:
>   1. Patient is Māori or of any Pacific ethnicity; or
>   2. Patient has pre-existing cardiovascular disease or risk equivalent*; or
>   3. Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator; or
>   4. Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult; or
>   5. Patient has diabetic kidney disease**; and
> 3. ~~Target HbA1c (of 53 mmol/mol or less) has not been achieved despite the regular use of~~ **Has regularly used** one blood-glucose lowering agent (metformin, vildagliptin or insulin) for at least 3 months~~-~~
>
> Note: criterion 3.1-3.5 intended to describe patients at high risk of cardiovascular or renal complications of diabetes.
> * Pre-existing cardiovascular disease or risk equivalent defined as: cardiovascular disease event (angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack, ischaemic stroke, peripheral vascular disease), congestive heart failure or familial hypercholesterolaemia.
> ** 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).

7.4. In making this recommendation, the Committee considered:

- that the intent of widening access to empagliflozin was to enable more people to benefit from the lowering of the risk of cardiovascular and renal complications that is associated with empagliflozin.
- the high unmet health need for individuals who are not currently eligible for empagliflozin under the current HbA1c threshold, but have established cardiovascular disease or a high risk for cardiovascular disease.
- the potential to achieve more equitable health outcomes by improving diabetes-related outcomes for Māori and Pacific peoples with T2DM.
- the applicability of the available evidence on the benefits associated with SGLT2 inhibitors to individuals with an HbA1c level of less than 53mmol/L.
- the impact of delaying time to renal replacement therapy on the health sector.

7.5. GLP-1 agonists

- The Advisory Committee **recommended** that access to GLP-1 agonists be amended to remove the HbA1c threshold be **declined**.
- In making this recommendation, the Advisory Committee considered that there was insufficient evidence at the time to suggest that there would be a health benefit associated with removing the HbA1c threshold for funded access to GLP-1

agonists.

Discussion

Māori impact

7.6. The Committee discussed the impact of removing the HbA1c threshold from the empagliflozin Special Authority on Māori health areas of focus and Māori health outcomes. The Committee noted that matehuka (diabetes) is one of Pharmac's Hauora Arotahi (Māori health areas of focus). The Committee considered that removing the HbA1c criteria would enable more Māori with T2DM to access empagliflozin and experience a lowering of cardiovascular and renal risk.

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

7.7. The Committee discussed the impact of removing the HbA1c threshold from the empagliflozin Special Authority on Pacific peoples' health outcomes. The Committee noted that Pacific peoples are disproportionately affected by T2DM and removing the HbA1c criteria for funded access to empagliflozin would enable more people of Pacific ethnicity to experience the cardiovascular and renal benefits associated with empagliflozin.

7.8. The Committee considered there was a lack of evidence to assess the impact of type 2 diabetes among disabled people, tāngata whaikaha Māori and people who have been underserved by the health system. The Committee considered that groups in the community who experienced inequitable access to primary care were less likely to receive screening and other appropriate care for the management of type 2 diabetes.

Background

7.9. The Committee noted that empagliflozin for individuals with T2DM and high cardiovascular risk and/or Māori or Pacific ethnicity, and/or renal disease was listed on the Pharmaceutical Schedule on 1 February 2021.

7.10. The Committee noted that a dulaglutide for individuals with T2DM and established cardiovascular disease was listed on 1 September 2021. The Committee also noted that, due to supply issues affecting dulaglutide and GLP-1 agonists more generally, liraglutide as an alternative to dulaglutide was listed on 1 March 2023.

7.11. The Committee noted that the present application was for a removal of the HbA1c threshold associated with funded access to empagliflozin and GLP-1 agonists. The Committee noted that it had previously considered a widening of access to liraglutide, a GLP-1 agonist, in November 2022.

7.12. The Committee considered that the intent of widening access to empagliflozin was to enable a broader group of people to benefit from a lowering of the cardiovascular and renal risk associated with empagliflozin.

Health need

7.13. The Committee noted that it had previously considered the health need of individuals with T2DM across a range of meetings in November 2017 (empagliflozin) and February 2019 (dapagliflozin, anti-diabetic agents).

7.14. The Committee noted that the Diabetes and Cardiovascular Advisory Committees provided advice on the health need of individuals with T2DM in March and May 2019 in their respective assessment of treatments for diabetes and treatments with cardiovascular benefits in this population. The Committee noted that many people with T2DM now have funded access to empagliflozin and GLP-1 agonists, but some individuals were not eligible for these agents because they had an HbA1c level of less than 53mmol/mol. The Committee considered that there was an unmet health need among the latter group.

7.15. The Committee noted HbA1c level is a marker of glycaemic control which is positively associated with the risk of macrovascular and microvascular complications. The Committee noted the current eligibility criteria for SGLT2-inhibitors and GLP1-agonists included an HbA1c threshold in the access criteria of 53mmol/mol. The Committee noted this 53mmol/mol threshold was recognised internationally as a target HbA1c threshold for glycaemic control used to guide treatment decisions with the intent of lowering the risk of diabetes-related complications.

7.16. The Committee noted that the data supporting the recommended HbA1c thresholds in clinical practice were established in European populations, with uncertain applicability to Māori and Pacific individuals. The Committee also considered that, due to a lack of accessible epidemiological data on HbA1c levels in New Zealand, it was difficult to estimate how many Māori or people of Pacific ethnicity with T2DM had HbA1c levels below the threshold of 53 mmol/mol.

Health benefit

Empagliflozin

7.17. The Committee noted that the key trials of SGLT inhibitors among individuals with T2DM such as CANVAS (canagliflozin), DEPICT-2 (dapagliflozin), and EMPA-REG (empagliflozin) included lower-end HbA1c thresholds for inclusion of 53, 57 and 53 mmol/mol, respectively. The Committee considered that the results of these trials could not be extrapolated to individuals with T2DM and HbA1c levels <53 mmol/mol.

7.18. The Committee considered that the assessment of likely benefits associated with SGLT2 inhibitors among individuals with T2DM and HbA1c levels below 53mmol/mol would need to rely on indirect evidence by means of subgroup analyses of groups with different HbA1c levels within the key trials, evidence from trials of SGLT2 inhibitors among individuals without diabetes, and non-experimental observational evidence on the benefits associated with lowering HbA1c levels below the 53mmol/mol threshold.

7.19. The Committee noted that some of the earliest evidence of the benefits associated with lowering HbA1c in the setting of T2DM came from the United Kingdom Prospective Diabetes Study (UKPDS), a trial of metformin in addition to conventional therapy which reported that HbA1c, a measure of glycaemic control, was associated with the risk of both microvascular and macrovascular complications among this study population. The Committee noted that the greatest microvascular and macrovascular risks were experienced by participants with HbA1c levels above 7% (53 mmol/mol) and this was subsequently reflected in many of the clinical guidelines on glycaemic control in diabetes.

7.20. The Committee noted a meta-analysis of observational studies, which reported a non -linear relationship between HbA1c and all-cause mortality among individuals with T2DM, with the greatest increases in mortality risk observed at the most elevated HbA1c levels (Arnold & Wang. Rev Diabet Stud. 2014;11:138-152). The Committee considered this meta-analysis to be suggestive of the potential survival benefits associated with additional lowering of HbA1c among individuals with HbA1c levels already below 53 mmol/mol. The Committee considered that these individuals may experience a smaller absolute magnitude of benefit compared to individuals with HbA1c levels above 53 mmol/mol.

7.21. The Committee considered that HbA1c was not always a comprehensive predictor of clinical endpoints. The Committee noted that in UKPDS, the differences in HbA1c levels between the two trial arms did not persist beyond a year after the trial period. However, participants in the metformin arm continued to experience a reduced risk of macrovascular events, diabetes-related complications, and all-cause mortality at 10 years follow-up compared to those in the conventional treatment arm (Holman et al. N Engl J Med. 2008;359:1577-89). The Committee considered metformin and other diabetes treatments may be associated with health benefits which are not completely reflected in the level of long-term glycaemic control for individuals with T2DM.

7.22. The Committee considered evidence that dapagliflozin, an SGLT2-inhibitor, and metformin were associated with similar reductions in HbA1c levels relative to baseline, and that combined use of the two agents was associated with greater HbA1c reductions compared to either agent used alone (Henry et al. Int J Clin Pract.2012;66:446-56).

7.23. The Committee noted an observational study, comparing SGLT2-inhibitors to metformin as first-line therapy for the management of T2DM, which reported that SGLT2 inhibitors were associated with lower risk of all-cause mortality over the 12-month follow-up period compared to metformin (HR 0.49, 95% CI 0.44-0.55, p<0.0001) (Chen et al. Cardiovasc. Diabetol. 2020;19:189).

7.24. The Committee noted a meta-analysis which reported that treatment with SGLT2 inhibitors results in clear and consistent reductions in cardiovascular, kidney and mortality outcomes regardless of whether patients are receiving or not receiving metformin. (Neuen et al. 2021;23:382-390). The Committee considered that the applicability of these results to individuals with T2DM and an HbA1c level <53 mmol/mol was uncertain.

7.25. The Committee noted evidence from some randomised controlled trials which suggested that SGLT2 inhibitors may be associated with a similar range and relative magnitude of health benefits between individuals with T2DM and HbA1c ≥ 53 mmol/mol at baseline and individuals with T2DM and an HbA1c level <53 mmol/mol.

7.26. The Committee noted that EMPA-REG included a subgroup analysis of participants who had baseline HbA1c levels of 53-64 mmol/mol and >64 mmol/mol, and that the point estimates for relative risk of cardiovascular death were similar between the groups ([≥8.5% HR 0.69, CI 0.46-1.03] and [<8.5% HR 0.59, CI 0.45-0.77] for both, $p_{interaction}$<0.51).

7.27. The Committee noted that EMPA-KIDNEY, a trial of empagliflozin among individuals with kidney disease, with or without diabetes, reported that empagliflozin was associated with a similar relative risk reduction compared to placebo for the primary composite outcome of progression of kidney disease or death from cardiovascular causes between groups of participants who had different baseline HbA1c levels;

HbA1c <39 mmol/mol (HR 0.77, 95% CI 0.63-0.94), HbA1c ≥39<48 mmol/mol (HR 0.75, 95% CI 0.58-0.96) and HbA1c ≥48mmol/mol (HR 0.65, 95% CI 0.52-0.81).

7.28. The Committee noted an observational study of a cohort with T2DM receiving SGLT2 inhibitors which reported that SGLT2 inhibitors were associated with reduced rates of eGFR decline during the two-year follow-up period compared to the period prior to receiving SGLT2 inhibitors. The Committee noted that the study reported a greater magnitude reduction in eGFR decline among the group who had baseline HbA1c levels of less than 7.5% compared to the group with baseline HbA1c levels greater than 7.5% (Cheung et al. Diabetes Res Clin Pract. 2023;195:110203).

7.29. The Committee noted a meta-analysis of SGLT2 inhibitor trials, conducted among participants without diabetes, which reported that SGLT2 inhibitors were associated with a reduced risk of cardiovascular deaths and heart failure compared to placebo (risk ratio 0.78; p<0.001) (Teo et al. J Am Heart Assoc. 2021;10:e019463).

7.30. The Committee noted a meta-analysis of SGLT2 inhibitor trials which reported that SGLT2 inhibitors were associated with similar relative risk reductions of kidney disease progression and of cardiovascular death among individuals with and without diabetes. The Committee noted that this same meta-analysis reported that SGLT2 inhibitors were associated with reduced all-cause mortality compared to placebo among individuals with diabetes, but this same association was not observed among individuals without diabetes (Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Lancet. 2022;400:1788-1801)

7.31. The Committee considered that the available clinical evidence indicated that empagliflozin may be associated with a similar range of cardiorenal health benefits for individuals with T2DM and HbA1c levels of <53 mmol/mol compared to individuals with higher HbA1c levels. The Committee considered that the available evidence suggested SGLT2 inhibitors may offer a smaller all-cause mortality benefit among individuals with T2DM and HbA1c levels of <53 mmol/mol compared to individuals with higher HbA1c levels, and the strength and quality of evidence to support this benefit was substantially lower compared to the evidence for improved cardiorenal outcomes.

Dulaglutide

7.32. The Committee noted the REWIND (dulaglutide), SUSTAIN-6 (semaglutide), LEADER (liraglutide), and PIONEER (semaglutide) trials included individuals with HbA1c thresholds of ≥53 mmol/mol. The ELIXA and EXSCEL trials included individuals with 42 and 49 mmol/mol, respectively.

7.33. The ELIXA (lixisenatide) trial indicated GLP-1 agonists were more effective in reducing HbA1c and body weight compared to placebo, however there were no additional health benefits experienced by individuals with T2DM with a recent acute coronary event receiving GLP-1 agonist compared with placebo, and no stratified analyses of outcomes based on HbA1c concentrations were conducted.

7.34. The EXSCEL (exenatide) trial reported individuals with T2DM with or without previous cardiovascular disease who received a GLP-1 agonist experienced greater reduction body weight, HbA1c levels and blood pressure compared to placebo, however no additional health benefits were experienced and there was no difference in primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) for individuals with HbA1c levels <53 or ≥53

mmol/mol. The Committee considered that all-cause mortality was reduced across the whole study population when using a GLP-1 agonist (HR= 0.86, 95% CI; 0.77-0.97), however the number-needed-to-treat would be >300. The Committee considered there to be high-quality indirect evidence that GLP-1 agonists provide weight loss benefits for individuals with T2DM with controlled glycemia.

7.35. The Committee noted there is no clinical evidence indicating health benefit of GLP-1 agonists for non-diabetic individuals with high cardiorenal risk. The Committee considered there to be insufficient data to determine where there are health benefits for individuals with T2DM and an HbA1c level <53 mmol/mol.

7.36. The Committee noted an observational study reporting that the addition of a GLP-1 agonist to metformin is less cardioprotective than the addition of a SGLT2 inhibitor (Deremer et al. Diabetes Complications. 2021;35:107972).

Cost and savings

7.37. The Committee considered that removing the HbA1c threshold for funded access to SGLT2 inhibitors would substantially increase the number of individuals eligible for these medicines. The Committee considered that this reflected the size of the population in New Zealand who had an unmet health need with regard to cardiovascular and renal risk and could benefit from additional lowering of HbA1c levels.

7.38. The Committee considered that if the HbA1c threshold were to be removed, the main determinants of an individual with T2DM eligibility for empagliflozin would be their five -year cardiovascular event risk or their ethnicity. The Committee noted that in New Zealand, clinicians in primary care conduct cardiovascular event risk assessments using an algorithm derived from the PREDICT study. The Committee noted that the current algorithm does not include an HbA1c component, but new versions of the risk assessment algorithm may include such a component, and this may have some implications for the proportion of individuals with T2DM who are assessed as being at high cardiovascular risk.

7.39. The Committee considered that, based on evidence of empagliflozin use in other settings, empagliflozin may be associated with reduced hospitalisation rates and delayed time to requiring renal replacement therapy in some individuals.

Summary for assessment

7.40. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for empagliflozin if it were to be funded in New Zealand for T2DM irrespective of glycemia. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with T2DM who have high cardiovascular/cardiorenal risk (or are Māori or of any Pacific ethnicity) and controlled HbA1c (ie. 53 mmol/mol or less).
Intervention	Empagliflozin, 10 mg or 25 mg tablet once daily, treatment ongoing. Taken either as adjunctive treatment with metformin, or first-line instead of metformin

+Comparator(s)	Metformin (if tolerated at therapeutic doses)
Outcome(s)	Reduction in cardiovascular events / cardiorenal risk

Table definitions:

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

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

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

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

8. Empagliflozin, chronic kidney disease, non-diabetic

Application

8.1. The Committee reviewed the application for empagliflozin in the treatment of non-diabetic chronic kidney disease (CKD).

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

Recommendation

8.3. The Committee **recommended** that empagliflozin be listed with a **high priority** subject to the following Special Authority criteria:

Empagliflozin

Initial application – application from any relevant practitioner. Valid for 12 months.

1. Patient has non-diabetic chronic kidney disease; and
2. Patient is receiving the maximum tolerated dose (unless contraindicated) of ACE inhibitor or angiotensin receptor blocker; and
3. Either:
   a. Patient has estimated glomerular filtration rate of 20-45 mL/min/1.73m^2 or;
   b. Both
      i. Patient has estimated glomerular filtration rate of 45-90 mL/min/1.73m^2 and;
      ii. Patient has a urinary albumin-to-creatinine ratio of at least 20 mg/mmol.

Renewal application. Valid for 12 months.

1. Treatment continues to be appropriate.

8.4. In making this recommendation, the Committee considered:

8.4.1. the high health need of individuals with CKD, especially among those who may eventually require renal replacement therapy.

8.4.2. the health need of carers, family and whānau of people with CKD, especially among those who may eventually require renal replacement therapy.

8.4.3. the clinical evidence indicating that empagliflozin is associated with delayed progression of CKD and lower all-cause hospitalisation compared to standard of care treatment, among individuals with CKD, irrespective of diabetes status.

8.5. The Committee considered that further advice could be sought from the Nephrology Advisory Committee on whether the proposed access criteria for empagliflozin could

be amended to better target priority populations, and whether the proposed eGFR and uACR thresholds were clinically appropriate.

Discussion

Māori impact

8.6. The Committee discussed the impact of funding empagliflozin for the treatment of non-diabetic CKD on Māori health areas of focus and Māori health outcomes. The Committee noted that the prevalence of CKD is greater among Māori compared with non-Māori, non-Pacific populations. The Committee noted that the incidence rate for end-stage kidney disease (ESKD) is 255 people per million among Māori. The Committee noted Māori with kidney failure are significantly less likely to receive a kidney transplant and the mortality rate for people with kidney failure was estimated to be 181 per million among Māori.

8.7. The Committee noted Māori experience whakamā (*disempowerment and embarrassment*) due to delayed diagnosis, missed opportunities for preventive care and regret and self-blame. The Committee noted that Māori also experience stigma associated with CKD, can have a multigenerational fear of dialysis and an awareness that clinicians are not aware of cultural considerations and values during decision-making for management of CKD.

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

8.8. The Committee discussed the impact of funding empagliflozin for the treatment of non-diabetic CKD on Pacific peoples and noted that the prevalence of CKD is greater in Pacific peoples compared with non-Pacific peoples and non-Māori individuals. The Committee noted that the incidence rate for ESKD is 340 people per million for Pacific peoples, no renal transplants were received by Pacific peoples in 2020, and the mortality rate for kidney failure was estimated to be 242 per million among Pacific peoples.

8.9. The Committee considered there was a lack of evidence to assess the impact of CKD among disabled people, tāngata whaikaha Māori and people who have been underserved by the health system. The Committee considered that groups in the community who experienced inequitable access to primary care were less likely to receive screening and other appropriate care for the management of CKD.

Health need

8.10. The Committee noted that CKD is an irreversible long-term condition that adversely affects the kidney structure and function, compromising the kidneys' ability to filter toxins from the blood and excrete waste products via urine.

8.11. The Committee noted the severity of CKD can be determined by the estimated glomerular filtration rate (eGFR), which indicates the level of kidney function or by the presence of albumin in the urine (albuminuria), indicating the level of kidney damage. The Committee noted the funding application for empagliflozin for non-diabetic kidney disease was for people with mild to moderate CKD with macroalbuminuria (>20 mg/mmol) and for people with moderate to severe CKD.

8.12. The Committee noted that, especially in the earliest stages, CKD often remains underdiagnosed because the initial decline in kidney function can be asymptomatic.

The Committee noted that the complications of CKD included volume overload, hyperkalaemia, metabolic acidosis, hypertension, anaemia, and mineral and bone disorders. The Committee noted that although symptoms can be managed with medications and other clinical interventions, the decline in kidney function associated with CKD is irreversible and usually inexorable.

8.13. The Committee noted that the rate of progression of CKD from one major stage to another varies based upon the underlying disease, presence of comorbid conditions, the available treatments, socioeconomic status, individual genetics, ethnicity, and other factors. The Committee noted that the intent of treatment of CKD is to slow the rate of progression and thereby delay or prevent individuals from developing ESKD and requiring renal replacement therapies such as dialysis or a kidney transplant.

8.14. The Committee noted that the global prevalence of CKD is estimated to be between 11-13%. The Committee noted it is difficult to estimate the number of individuals with non-diabetic CKD in New Zealand as the disease is initially asymptomatic and screening rates for the condition are highly variable across the country. The Committee noted two regional New Zealand studies which estimated the prevalence of CKD to be 13% and 11.8%, respectively (Tafuna'i et al. Nephrology [Carlton]. 2022;27:248-59, Lloyd et al. Nephrology. 2019;24:308-15).

8.15. The Committee noted that, in the Southland region in 2014, the prevalence of CKD among Māori was higher compared to New Zealand Europeans (adjusted odds ratio [aOR] =1.56 [95% CI 1.45 to 1.69]) (Lloyd et al. 2019). The Committee noted a clinic-based observational study conducted among individuals registered at two Pacific health providers in Auckland, which reported that in 2017 the prevalence of CKD was 10.4% for Māori participants compared to 7.1% of non-Māori, non-Pacific participants (Tafuna'i et al. 2022).

8.16. The Committee noted that, in the Southland region in 2014, the prevalence of CKD among Pacific peoples was higher compared to New Zealand Europeans (aOR=2.62 [95% 2.28 to 3.01]) (Lloyd 2019). The Committee noted that, based on a clinic-based observational study, the prevalence of CKD among Pacific peoples was estimated to be between 15.5 and 21.8 % in 2017, with some variation between different Pacific ethnicities (Tafuna'i et al. 2022).

8.17. The Committee noted that in 2020, there were 3,004 individuals receiving renal replacement therapy in New Zealand and that this number has grown over time. The Committee noted that the crude incidence of initiating renal replacement therapy was estimated to be 253 per million among Māori, 475 per million among Pacific peoples and 79 per million among people of European and other ethnicities (Australia and New Zealand Dialysis and Transplant Registry [ANZDATA]. Annual Report. 2021).

8.18. The Committee noted Māori and Pacific peoples with ESKD experience inequitable access to kidney transplant compared with non-Māori, non-Pacific peoples (ANZDATA, 2021).

8.18.1. The Committee noted that in 2020, the mortality rate for people with kidney failure was estimated to be 181 per million among Māori compared to 53 per million among non-Māori, non-Pacific peoples, which is likely to reflect Māori having lower kidney transplantation rates and a higher prevalence of cardiovascular-associated causes of death than Pacific and non-Māori and non-Pacific populations (ANZDATA, 2021).

8.18.2. The Committee noted that there were no transplants undertaken in Pacific peoples (prior to staring dialysis) in 2020 and the mortality rate for people with kidney failure was estimated to be 242 per million among Pacific peoples (ANZDATA, 2021).

8.19. The Committee noted that Māori and Pacific peoples are more likely to be started on dialysis with haemodialysis, more likely to be provided with facility-based dialysis as the principal modality of care, and experience less home-based dialysis modalities compared with non-Māori, non-Pacific peoples (ANZDATA, 2021).

8.20. The Committee noted the history of systemic bias in the formulae used to estimate GFR. The Committee noted that internationally there were three formulae used to estimate GFR: the Cockcroft and Gault formula, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and the Modification of Diet in Renal Disease (MDRD) equation. These formulae were developed from predominantly European populations and that the CKD-EPI equation included a race coefficient of 1.212, and that this multiplier was applied to individuals identified as African American. The Committee noted that this coefficient was based on false notions of African Americans having higher lean mass than people of other ethnicities. The Committee noted a growing body of validation studies of eGFR formulae which support the view that there is no biological or other basis to include race-based or ethnicity-based criteria in these formulae.

8.21. The Committee noted that a race-adjusted CKD-EPI formula was used to determine trial eligibility in EMPA-KIDNEY and that internationally either the CKD-EPI or the MDRD were most commonly used to calculate eGFR. The Committee noted that the Cockcroft and Gault formula had fallen out of favour in recent years as it was less reliable in predicting GFR compared to the other two formulae.

8.22. The Committee considered that in New Zealand, most laboratories use the MDRD to estimate GFR. The Committee noted that pre-2021 versions of the MDRD included a waist circumference criterion, causing the formula to artificially overstate the eGFR among people of ethnicities with higher average waist circumferences such as Māori, Pacific peoples and other people of non-European ethnicity. The Committee considered that this systemic bias in the way eGFR was calculated has resulted in historic harm to these groups, noting that many could have been denied appropriate care because their renal function was being overstated by the MDRD.

Health benefit

8.23. The Committee noted empagliflozin is an inhibitor of sodium glucose co-transporter 2 (SGLT2) which is found in the proximal tubules in the kidneys. Empagliflozin prevents renal reabsorption of glucose, resulting in improvement glycaemic control. The Committee noted that individuals require adequate renal function to initiate empagliflozin.

8.24. The Committee noted the EMPA-Kidney trial in which 6609 individuals with CKD were randomised to receive empagliflozin or placebo as an add-on to their standard treatment of care; 54% of individuals had non-diabetic CKD. There were 432 participants (13.1%) in the empagliflozin group and 558 participants (16.9%) in the placebo group (hazard ratio (HR), 0.72; 95% confidence interval (CI) 0.64 to 0.82; P<0.001) experienced the primary composite outcome of sustained decline of >40% in eGFR, onset of ESKD or death due to renal or cardiovascular causes. Hospitalisations due to any cause were experienced at rates of 24.8 hospitalisations per 100 patient years for individuals receiving empagliflozin and 29.2 hospitalisations

per 100 patient years for individuals receiving placebo (HR: 0.86; 95% CI 0.78 to 0.95, P=0.003). Progression of kidney disease was experienced by 384 (11.6%) of individuals receiving empagliflozin and 504 (15.2%) individuals receiving placebo. 59 (1.8%) individuals receiving empagliflozin and 69 (2.1%) of individuals receiving placebo (HR: 0.84; 95% CI 0.60 to 1.19) died due to cardiovascular causes during the trial.

8.25. The Committee noted the DAPA-CKD trial in which 4304 individuals with CKD were randomised to receive dapagliflozin or placebo as an add-on to their standard treatment of care, 32.5% of individuals had non-diabetic CKD. Irrespective of diabetes status, the event rate for the primary outcome (defined as: sustained decline of >50% in eGFR, onset of ESKD or death due to renal or cardiovascular causes) was lower in the dapagliflozin group, (5.2 events per 100 patient-years) compared to the placebo group (8.0 events per 100 patient-years); the HR was 0.64 (95% CI 0.52–0.79). There was no significant interaction between diabetes status and the primary composite outcome ($P_{interaction}$=0.24). For participants without diabetes, the event rate for the primary outcome was also lower in the dapagliflozin group (3.4 events per 100 patient-years) than in the placebo group (6.3 events per 100 patient-years); the HR was 0·50 (0·35–0·72). For participants without diabetes ESKD was experienced at rates of 2.4 events per 100 patient-years for individuals receiving dapagliflozin and 3.9 events per 100-patient years for individuals receiving placebo (HR 0.56 [95% CI 0.36-0.87]). For participants without diabetes eGFR declining to < 15 mL/min per 1.73m^2 was experienced at rates of 2.0 events per 100 patient-years for individuals receiving dapagliflozin and 3.2 events per 100-patient years for individuals receiving placebo (HR 0.56 [95% CI 0.35-0.91]). Individuals without diabetes requiring chronic dialysis was experienced at a rate of 1.5 events per 100 patient-years for individuals receiving dapagliflozin and 2.1 events per 100-patient years for individuals receiving placebo (HR 0.62 [95% CI 0.36-1.09]).

8.26. The Committee noted a systematic review and meta-analysis in which 90,409 individuals with CKD including 15,605 (17.3%) without diabetes received an SGLT inhibitor. The study reported that the risk of kidney disease progression was reduced for those treated with an SGLT2 inhibitor compared with placebo by 37% (relative risk [RR] 0·63, 95% CI 0·58–0·69) with similar RR in patients with and without diabetes. In the four chronic kidney disease trials, RR were similar irrespective of primary kidney diagnosis. SGLT2 inhibitors reduced the risk of acute kidney injury by 23% (0·77, 95% CI 0·70–0·84) and the risk of cardiovascular mortality or hospitalisation or heart failure by 23% (0·77, 95% CI 0·74–0·81), again with similar effects in those with and without diabetes. SGLT2 inhibitors also reduced the risk of cardiovascular death (0·86, 95% CI 0·81–0·92) but did not significantly reduce the risk of all-cause mortality (0·94, 95% CI 0·88–1·02). For these mortality outcomes, RR were similar in patients with and without diabetes. For all outcomes, results were broadly similar irrespective of what the individuals eGFR was prior to starting the trial. Based on estimates of absolute effects, the absolute benefits of SGLT2 inhibition outweighed any serious hazards of ketoacidosis or amputation (Nuffield Department of Population Health Renal Studies Group and SGLT2 inhibitor Meta-analysis Cardio-Renal Trialists' Consortium. Lancet. 2022;400:1788-801).

8.27. The Committee noted evidence from the following studies:

8.27.1. Vart et al. Clin J Am Soc Nephrol. 2022: 17: 1754-62

8.27.2. McEwan et al. Clin J Am Soc Nephrol. 2022;17:1730-41

8.27.3. Waijer et al. Diabetologia, 2022;65:1085-97

8.27.4. Heerspink et al. Lancet Diabetes Endocrinol. 2021;9:743-54

8.28. The Committee considered there to be a class-effect across SGLT2 inhibitors as an add-on therapy for the treatment of CKD, with key trials across empagliflozin, dapagliflozin and canagliflozin reporting similar magnitudes of treatment benefit in this setting. The Committee considered that dapagliflozin may be slightly more efficacious than empagliflozin and canagliflozin, based on the available evidence. The Committee considered however that differences in reported efficacy between SGLT2 inhibitor trials could have been driven by differences in baseline characteristics of trial participants.

8.29. The Committee considered the evidence to support use of empagliflozin in CKD to be of high quality and moderate strength. The Committee noted that EMPA-KIDNEY reported broadly similar magnitudes of reduced kidney disease progression associated with empagliflozin among different subgroups of different eGFR status and diabetes status.

8.30. The Committee noted that the EMPA-KIDNEY had a median follow-up duration of two years and noted that some of the secondary outcomes the trial reported such as cardiovascular mortality occur over timescales much longer than this. The Committee considered that such a short length of follow-up in the trial meant that the longer-term trajectory of these outcomes would need to be extrapolated from limited clinical data, introducing uncertainty in the Committee's assessment of the ultimate likely treatment benefit associated with empagliflozin. The Committee considered this would especially be the case for understanding the benefits associated with empagliflozin among individuals with earlier stage CKD, who were likely to be on treatment for longer and could potentially experience the greatest delays in time to requiring either additional care for CKD complications or renal replacement therapies.

8.31. The Committee considered that empagliflozin would provide a health benefit to family, whānau and wider society, by slowing the progression of CKD and in turn delaying the need for individuals to receive renal replacement therapy or treatment for CKD-related complications. The Committee considered that this may improve the health-related quality of life of family and whānau, by reducing the burden of care associated with dialysis or hospital admissions.

Suitability

8.32. The Committee noted that empagliflozin is an oral medication that is administered once daily, in addition to other community funded medications. The Committee noted that funding empagliflozin may exacerbate issues relating to polypharmacy given many individuals will already have a considerable pill burden from medicines they are taking either for CKD or other comorbidities.

Cost and savings

8.33. The Committee considered that there could be over 260,000 people in New Zealand with CKD, based on the 2014 prevalence of roughly 5% reported in Lloyd et al. 2019, and it was possible that in the intervening period that the prevalence had further increased from this level. The Committee considered that a large proportion of these individuals would be eligible for empagliflozin under the proposed access criteria.

8.34. The Committee noted that some individuals with CKD may have diabetes and be eligible for funded empagliflozin under current Special Authority criteria (i.e., HbA1c ≥ 53 mmol/ml despite three-month' trial of metformin, or metformin intolerance).

8.35. The Committee noted that CKD testing rates were variable around New Zealand, with testing rates ranging from 40% to 70% reported in different publications (Lloyd et al. 2019; Tafuna'i et al. 2022). The Committee considered that rates of eGFR and uACR testing in primary care would increase if access to empagliflozin were to be widened, as primary care clinicians would be encouraged to screen high-risk individuals for CKD to see if they are eligible for empagliflozin. The Committee considered that a whole-of-system approach was needed to support screening for CKD in primary care and equitable uptake of empagliflozin, particularly for Māori, Pacific peoples and other groups disproportionately impacted by CKD. The Committee considered there is a risk that, despite strong initial uptake, persistence might wane due to the asymptomatic nature of CKD for many people and that prescriber education, follow-up mechanisms and consumer awareness of the importance of remaining on treatment would also be important.

8.36. The Committee noted that funding empagliflozin for CKD may slow the rate at which individuals progress to requiring renal replacement therapies such as dialysis. The Committee noted that dialysis and other renal replacement therapies were associated with very high costs to the health sector and delaying the time before people require such therapies could result in savings to the health sector.

8.37. The Committee noted that a key component of the economic assessment of empagliflozin was the range of cardiovascular and survival health benefits that could be reasonably inferred from a reduced risk of kidney disease progression. The Committee noted that EMPA-KIDNEY reported a range of secondary outcomes, some of which could reasonably be expected to be associated with reduced CKD progression but none of the results for these endpoints were statistically significant.

8.38. The Committee considered that it was reasonable to assume that a reduced risk of kidney disease progression would correspond to both a reduction in the risk of developing end-stage kidney disease and a reduction in the risk of cardiovascular mortality, and as such, these outcomes were appropriate to include in the PICO for economic assessment. The Committee noted that these outcomes occur over relatively long-time horizons, as such, it was unlikely that trial evidence would be available to inform the modelling of these endpoints.

Funding criteria

8.39. The Committee noted that in Australia, the access criteria for dapagliflozin excluded individuals with polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis. The Committee noted that the EMPA-KIDNEY trial excluded people with polycystic kidney disease. The Committee noted that people in New Zealand with polycystic kidney disease have a funded alternative in tolvaptan which reduces the long-term progression of the condition, however the Committee considered that people with polycystic kidney disease would still benefit from empagliflozin. The Committee considered that specific CKD conditions were not appropriate to exclude from the access criteria for empagliflozin in New Zealand.

8.40. The Committee considered that further advice should be sought from the Nephrology Advisory Committee on whether the proposed access criteria for empagliflozin could be amended to better target priority populations, and whether the proposed eGFR and uACR thresholds were clinically appropriate.

Summary for assessment

8.41. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for empagliflozin if it were to be funded in New Zealand for CKD, without 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.

Population	People with chronic kidney disease (without type 2 diabetes), with either: • eGFR between ≥20 mL and ≤45 mL per 1.73m^2 or • eGFR between > 45 and <90 mL per 1.73m^2 and macroalbuminuria (>= 20 mg/mmol)
Intervention	Empagliflozin, 10mg once daily. Taken as an adjunctive medication in addition to other funded medications for chronic kidney disease.
Comparator(s)	Concomitant funded medication for CKD, which may include the following community pharmaceuticals: • Angiotensin converting enzyme inhibitors • Angiotensin II receptor blockers • Calcium channel blockers • Loop diuretics • Glucose-lowering agents • Cholesterol-lowering agents • Anti-platelet agents
Outcome(s)	Reduced risk of kidney disease progression • EMPA-KIDNEY reported that empagliflozin treatment was associated with a reduced risk of kidney disease progression compared to placebo, among people with chronic kidney disease without type 2 diabetes (HR= 0.80, 95% CI 0.60 to 0.96) (EMPA-Kidney Collaborative Group. NEJM. 2022 [Figure S5]). The following outcomes may be reasonably inferred from a reduced risk of kidney disease progression: • Reduced risk of developing end-stage kidney disease • Reduced risk of cardiovascular mortality

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

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

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

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

9. Tocilizumab for giant cell arteritis

Application

9.1. The Committee reviewed the application for tocilizumab for the treatment of giant cell arteritis.

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

Recommendation

9.3. The Advisory Committee **recommended** funding of sub-cutaneous tocilizumab for the treatment of giant cell arteritis (GCA) with a **medium priority**, within the context of rheumatology treatments, subject to Special Authority criteria, to be advised on by the Rheumatology Advisory Committee.

9.4. In making this recommendation, the Advisory Committee considered:

- The high unmet health need associated with GCA due to the chronic nature of GCA, prolonged treatment with steroids, and serious morbidity associated with both GCA, and chronic corticosteroid use.
- The evidence of benefit of tocilizumab in sustaining remission and reducing oral corticosteroid dose in those with GCA, whilst noting that the optimal treatment duration is unclear and relapse rate, following abrupt discontinuation of tocilizumab, is high (approximately 50%).
- The suitability advantages of a subcutaneous treatment in reducing pressures on hospital infusion services by allowing people with GCA and/or their caregivers to administer treatment at home.

9.5. The Committee recommended Pharmac seek advice from the Rheumatology Specialist Advisory Committee regarding optimal treatment duration for tocilizumab for GCA, and Special Authority Criteria.

Discussion

Māori impact

9.6. The Committee discussed the impact of funding tocilizumab for the treatment of GCA on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori experienced a similar incidence of GCA to New Zealand Europeans (Nagarajah et al. Rheumatol Adv Pract. 2022;6:rkac040), however the Committee considered that outcome data comparing Māori to other populations was lacking. The Committee noted that nearly all cases of GCA are treated with high doses of prednisone for at least a year, and around 25% are still receiving treatment after five years (Lyne et al. Front Med (Lausanne). 2022;9:1057917). The Committee agreed with the Rheumatology Advisory Committee, who, in March 2023, considered that most of the comorbidities associated with corticosteroid use inequitably affect Māori, and thus considered that this should be taken into account when assessing alternative therapies such as tocilizumab. The Committee noted that GCA is not

included within Hauora Arotahi (Māori health area of focus) in Te Whaioranga, Pharmac's Māori Responsiveness Strategy.

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

9.7. The Committee noted the possible impact of funding tocilizumab for the treatment of GCA on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee was not aware of any groups experiencing health inequities disproportionately affected by GCA.

Background

9.8. The Committee noted that intravenous tocilizumab is currently funded in New Zealand for the treatment of cytokine release syndrome, rheumatoid arthritis, juvenile idiopathic arthritis (systemic and polyarticular), adult-onset Still's disease, idiopathic multicentric Castleman's disease, and moderate to severe COVID-19.

9.9. The Committee noted that the Rheumatology Advisory Committee reviewed an application for the funding of tocilizumab for the treatment of polymyalgia rheumatica (PMR) in March 2023, and recommended the application be deferred pending the availability of further evidence to define the intended population to treat, treatment duration, and the appropriate timing of when to start treatment. When making this recommendation, the Rheumatology Advisory Committee considered there was a high need to fund agents such as tocilizumab for GCA.

Health need

9.10. The Committee noted that GCA (previously known as Horton's disease or temporal arteritis) is a rare type of autoimmune chronic systemic vasculitis (inflammation of the blood vessels) that typically affects the cranial arteries (especially the temporal and ophthalmic arteries), and less commonly the branches of the aorta (Borchers et al. Automimmun Rev. 2012;11:544-54). The Committee noted that GCA is characterised by granulomatous inflammation of the three-layered vessel wall that results in vaso-occlusion, wall dissection, and aneurysm formation (Weyand et al. Circ Res. 2023;132:238-50). The Committee noted that although the exact cause of GCA is unknown, the pathophysiology involves a multi-step process with a pronounced acute phase response involving pro-inflammatory cytokines, in particular IL-6 which is an important mediator of inflammation (Borchers et al. Autoimmun Rev. 2012;11:544-54, Steel et al. Drugs Aging. 2015;32:591-9).

9.11. The Committee noted that PMR is closely linked to GCA, occurring in approximately 40-60% of people with GCA, although the precise nature of the relationship between GCA and PMR is not completely understood (bpac^{nz}. 2013;53:17-23). The Committee note that conversely, GCA is found in approximately 15-20% of people with PMR (Li et al. Arthritis Res Ther. 2021;23:82).

9.12. The Committee noted that the incidence of GCA increases with age, most commonly affecting people aged over 50 years, and is two to three times more common in females than males (Borchers et al. Autoimmun Rev. 2012;11:544-54, Steel et al. Drugs Aging. 2015;32:591-9).The Committee noted that from the literature, the highest reported rates of GCA are in northern Europe (especially in people of Scandinavian descent), although it can also affect other groups (Gonzalez-Gay et al. Arthritis Rheum. 2009;6:1454). The Committee noted that the estimated incidence of GCA in New Zealand is 12.73 per 100,000 New Zealanders (Abdul-Rahman et al. N

Z Med J. 2011;124:44-52), around 270 people are expected to be diagnosed with GCA each year in New Zealand.

9.13. The Committee noted that Māori experience similar incidence of GCA to New Zealand Europeans (Nagarajah et al. Rheumatol Adv Pract. 2022;6:rkac040), however considered that outcome data comparing Māori to other populations is lacking. The Committee noted that nearly all cases of GCA are treated with high doses of prednisone for at least a year, and around 25% are still receiving treatment after five years (Lyne et al. Front Med (Lausanne). 2022;9:1057917). The Committee considered that steroid use differs between ophthalmology and rheumatology with visual problems caused by GCA requiring higher dose steroids The Committee agreed with the comments from the Rheumatology Advisory Committee in March 2023, that most of the comorbidities associated corticosteroid use inequitably affect Māori, and thus considered that this should be accounted for when assessing alternative therapies such as tocilizumab.

9.14. The Committee noted that the onset of symptoms in GCA tend to be subacute, but abrupt presentations over a few days can occur. The Committee noted that temporal headache is the most frequent symptom of GCA and will be present in approximately 75% of cases. The Committee noted that systemic features, including low-grade fever, anorexia, and fatigue are present in approximately half of those affected (bpac nz. 2013;53:17-23). The Committee noted that if undetected, GCA can have catastrophic sequelae, such as irreversible visual loss, stroke, and aortic aneurysm development. The Committee noted that loss of vision can be permanent, and large-vessel stenosis, and with it an increased risk of stroke, occurs in 10-15% of people (Kermani et al.. Ann Rheum Dis. 2013;72:1989-94).

9.15. The Committee noted that current treatment of GCA aims to dampen the acute inflammatory process, thereby preventing ischemic complications, prevent disease relapses using the lowest effective dose (if any) of corticosteroids, and prevent long-term vascular damage (ie aneurysm, vascular rupture, and stenosis) (Farina et al. Eur J Intern Med. 2023;107:17-26).

9.16. The Committee noted that the European Alliance of Associations for Rheumatology (EULAR) and British Society for Rheumatology (BSR) guidelines recommend starting treatment with high-dose corticosteroid therapy for a minimum of four weeks, gradually tapering the course, and adding methotrexate if flares occur.

9.17. The Committee considered that GCA can impact on the whānau of individuals with GCA due to the effect of the disease on friendships and relationships, the affected individual's ability to work, support children, and take part in recreational activities whilst symptomatic. The Committee considered that the chronic nature of GCA, prolonged treatment with steroids, and serious morbidity described all contribute to the currently high unmet health need of the condition.

Health benefit

9.18. The Committee noted tocilizumab is a humanised monoclonal antibody that targets the interleukin-6 (IL-6) receptor which is involved in immunological and inflammatory reactions. The Committee noted that only the subcutaneous formulation of tocilizumab is approved by Medsafe for the treatment of GCA in adults. The Committee noted that the recommended dose of tocilizumab for adults with GCA is 162 mg once weekly as a subcutaneous injection, in combination with a tapering course of corticosteroids. The Committee noted that tocilizumab may be used alone following discontinuation of corticosteroids. The Committee noted that tocilizumab is

currently recommended for the treatment of GCA in Australia, Canada, Scotland, and England/Wales. The Committee noted that tocilizumab does not treat GCA but rather dampens the inflammatory process.

9.19. The Committee noted that the applicant suggests that the current treatment algorithm (corticosteroid monotherapy) is altered to include tocilizumab for both new-onset (first line), and flare management (second line) treatment of GCA. The Committee considered agreed with the applicants view of the treatment algorithm. The Committee considered that patients not responding to current treatment would receive higher doses, and many patients would also receive methotrexate.

9.20. The Giant-Cell Arteritis Actemra (GiACTA) trial provided the primary evidence for tocilizumab for the treatment of GCA (Stone et al. 2017. N Engl J Med. 2017;377:317-28, Stone et al. Rheumatology (Oxford). 2022;61:2915-22, Adler et al. Rheumatology (Oxford).2019;58:1639-43, Strand et al. Arthritis Res Ther. 2019;21:64). The Committee noted that the trial was a phase III, randomised, double-blind, placebo-controlled, multicentre study of adult patients with either new onset or relapsing GCA (*N*=251) who were randomised in a 1:1:2:1 ratio to receive the following treatments for 52 weeks:

- Placebo subcutaneously (SC) weekly (QW) + 26-week prednisone taper regimen (PBO + 26 week; *n*=50)
- Placebo SC QW + 52-week prednisone taper regimen (PBO + 52 week; *n*=50)
- 162 mg tocilizumab SC QW + 26-week prednisone taper regimen (tocilizumab QW; *n*=100)
- 162 mg tocilizumab SC every other week (Q2W) + 26-week prednisone taper regimen (tocilizumab Q2W; *n*=50)

9.20.1. The Committee noted that after the 52-week double-blind treatment period (Part 1), all patients who had completed Part 1 of the study were eligible to enter the 104-week open-label extension of the study.

9.20.2. The Committee noted that the primary endpoint was proportion of patients in sustained remission from weeks 12 to 52 with adherence to a standardised 26-week (short course) corticosteroid taper compared with a 26-week corticosteroid taper given alone in the placebo group. The Committee noted that sustained remission at week 52 was 56% tocilizumab weekly (QW) and in 53% tocilizumab every two weeks (Q2W), 14% placebo group with 26-week prednisone taper and 18% in the placebo group with 52-week prednisone taper (*P*<0.001 for the comparisons of either active treatment with placebo).

9.20.3. The Committee noted the following results from secondary endpoints:

- Less prednisone used in the tocilizumab groups than placebo over 52 weeks.
- Fewer flares in the tocilizumab groups than placebo over 52 weeks, and over the 3-year extension period.
- In patients with new-onset and relapsing disease, the median time to first flare in the tocilizumab QW group was 577 and 575 days, respectively, vs 479 and 428 days with tocilizumab Q2W and 179 and 224 days with placebo.

9.20.4. The Committee noted that there was a mean increase of the 36-item short form survey (SF-36) quality of life measure in the groups that received tocilizumab, and a decreased SF-36 in groups that received placebo. The Committee noted that the improved quality of life was greater in the group that receive tocilizumab

weekly than in the group that received tocilizumab every two weeks.

9.21. The Committee considered that tocilizumab was a reasonably safe treatment for GCA, noting that no deaths occurred in the first 52 weeks of the GiACTA trial, and that withdrawal from the trial due to adverse events occurred in 6% of the patients in each tocilizumab group, 4% placebo with 26-week taper, and none in the other placebo group.

9.22. The Committee noted the results of a two-year open-label extension phase of the GiACTA trial and a previous phase II trial. The Committee considered these trials demonstrated that the relapse rate following abrupt discontinuation of tocilizumab is high, noting that more than 50% of those achieving remission on tocilizumab later relapsed once treatment was stopped (Adler et al. Rheumatology (Oxford).2019;58:1639-43, Stone et al. Lancet Rheumatol. 2021;3:e328-36). The Committee considered that there is currently insufficient evidence to define optimal duration of treatment and dosing schedule beyond 12 months for tocilizumab for GCA, but the above evidence suggested that treatment may need to be continued for longer than 12 months. The Committee considered that for people in remission after 12 months of treatment, a dose reduction of tocilizumab may be appropriate. However, the Committee noted that those from the extension study who received weekly (QW) tocilizumab experienced less flares, and improved quality of life in comparison to those who received tocilizumab every 2 weeks. (Calderon-Goerke et al, Clin Exp Rheumatol. 2023;41:829-36, Rakholiya et al. An Rheum Dis. 2021;80:655, Tomelleri et al. Semin Arthritis Rheum. 2023;59:152-74).

9.23. The Committee noted that there are differing recommendations on when to start tocilizumab for GCA; the American College of Rheumatology/Vasculitis Foundation (ACR/VF) recommended tocilizumab for all patients with newly diagnosed GCA, and the European Alliance of Associations for Rheumatology (EULAR) recommended tocilizumab in those with, or at risk of, corticosteroid-related adverse events or in patients who have relapsing disease. The Committee considered that New Zealand practice would likely align with the EULAR recommendations.

9.24. The Committee considered that the evidence for tocilizumab in GCA was of good quality due to the GiACTA trial's methodology and duration of the study.

9.25. The Committee noted that there is currently no data available on the use of intravenous tocilizumab for the treatment of GCA, although considered that it is expected that intravenous and subcutaneous tocilizumab are likely to provide the same or similar efficacy for this condition.

Suitability

9.26. The Committee noted that tocilizumab subcutaneous injections are available as pre-filled syringes and are self-administered. The Committee considered that individuals would require training for self-administration. The Committee noted that as per the Medsafe datasheet, the syringes require refrigeration, and once removed from the refrigerator can be stored up to 14 days at or below 30°C.

9.27. The Committee considered the advantages of the availability of a subcutaneous tocilizumab formulation for the treatment of GC. The Committee considered that a subcutaneous treatment would ease pressure on hospital and community infusion services, and allow people to self-administer, or have a caregiver help to administer at home which would improve access for people located rurally and/or unable to travel to infusion centre. Members noted that there would likely still be a health

system and personal cost for those people who require or prefer health-professional administration of subcutaneous treatment.

Cost and savings

9.28. The Committee considered that treatment of GCA with tocilizumab may reduce the cost of treating disease flares, including the number of healthcare practitioner visits. The Committee considered that treatment with high-dose long-term corticosteroids increases the risk of fractures, obesity, diabetes, cardiovascular disease, and serious infections; therefore, treatment that reduces the risk of these adverse effects is likely to result in health benefits and savings to the health sector.

9.29. The Committee considered that patient number and uptake estimates appeared reasonable.

9.30. The Committee considered it is difficult to estimate the cost of tocilizumab treatment due to the uncertainty regarding treatment duration. The Committee considered it likely that at least 50% of people would receive treatment beyond 12 months. The Committee considered there may be a cost for radiology services to assess blood vessel inflammatory response to treatment, and that there may be increased referrals to rheumatology services to access diagnosis and subsequent treatment.

Funding criteria

9.31. The Committee noted that future funding criteria would require a definitive diagnosis of GCA. The Committee considered that people may need to have completed a trial of methotrexate (3-6 months) before accessing tocilizumab. The Committee also considered that there should be a restriction surrounding corticosteroid dose tapering, suggesting that less than 10 mg was ineffective, despite a maximum appropriate dose of methotrexate.

Summary for assessment

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

9.33. The Advisory Committee noted that elements of in the PICO (population, intervention, comparator, outcomes) for this application is unclear/uncertain at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	individuals diagnosed with GCA
Intervention	Tocilizumab SC at dose of 162 mg once every week, in combination with a tapering course of corticosteroids.
Comparator(s) (NZ context)	Corticosteroids (eg oral prednisone 40-60 mg/day, tapered monthly with reductions depending on flare management and remission, methotrexate to a maximum of 20mg weekly
Outcome(s)	Reduced dose of corticosteroids Increased probability of sustained clinical remission at 52 weeks

	Increased time until first disease flare Improved health-related quality of life

Table definitions:

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

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

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

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

10. Infliximab, subcutaneous infliximab for the treatment of all current indications as intravenous infliximab

Application

10.1. The Committee reviewed the application for subcutaneous infliximab for the treatment of all currently funded indications as intravenous infliximab.

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 subcutaneous infliximab for the treatment of all currently funded indications as intravenous infliximab be listed with a **high priority,** the same Special Authority criteria.

10.4. The Committee recommended funding due to:

- Improved suitability of subcutaneous (self) administration for individuals
- Potential to improve equity of access for Māori, Pacific people and people with disability
- The significant benefit to the health system of freeing up infusion capacity in, constrained infusion services
- Acknowledging that the health benefit from the subcutaneous formulation is non inferior to the intravenous formulation.

Discussion

Māori impact

10.5. The Committee discussed the impact of funding subcutaneous infliximab for the treatment of all current indications as intravenous infliximab on Māori health areas of focus and Māori health outcomes.

10.6. The Committee noted Māori are known to have access inequity to funded medicines including access barriers to health care (including costs associated with primary care appointments, prescriptions, as well as access to and cost of transportation and obtaining time off work or childcare cover) and structural barriers (accessing

appointments and wait times)(Achieving access equity in Aotearoa New Zealand towards a theory of change, Pharmac, New Zealand Health Survey, Ministry of Health, 2022).The Committee considered the funding of subcutaneous infliximab would reduce some barriers including the time and cost of travelling to infusion centres.

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

10.7. The Committee discussed the impact of funding subcutaneous infliximab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted that the simple administration of subcutaneous infliximab, and its ability to be administered outside of infusion centres, may improve access through reduction in travel, and the ability to self-administer if thought appropriate by a medical practitioner.

Background

10.8. The Committee noted intravenous infliximab is currently funded for a range of indications and would need to remain as a funded option.

10.9. Pharmac staff sought advice regarding the benefits for the health system and those requiring treatment, and if the subcutaneous formulation were funded, if it provides the same health benefits as the currently funded intravenous infusions.

Health need

10.10. The Committee noted the health need of individuals with the indications currently receiving intravenous infliximab has previously been considered by the relevant Committees.

10.11. The Committee noted that those in rural areas experience inequities in accessing care, including increased travel time.

10.12. The Committee noted that there are currently substantial demands on intravenous infusion services resulting in delayed administration for some people, leading to an unmet need for treatment across a number of conditions.

Health benefit

10.13. The Committee noted infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα).

10.14. The Committee noted the following studies that evaluated the efficacy of intravenous infliximab compared to subcutaneous formulation in those with arthritis:

- Westhovens et al, Rheumatology (Oxford). 2021; 60: 2277-87
- X Baraliakos et al. Clin Case Rep. 2022;10:e05205
- Yoo et al. Arthritis Res Ther. 2016;18:82
- Yoo et al. Ann Rheum Dis. 2017;76:355-63
- Yoo et al. Ann Rheum Dis. 2013 Oct;72:1613-20

10.14.1. The Committee noted that there was no increase in the neutralising antibodies for the subcutaneous formulation of infliximab compared to the intravenous

formulation for those with rheumatoid arthritis.

10.14.2. The Committee considered that there were no differences in the safety profile the subcutaneous formulation of infliximab compared to the intravenous formulation for those with rheumatoid arthritis.

10.14.3. The Committee considered that the health benefit of the subcutaneous formulation in those with rheumatoid arthritis was non-inferior to the intravenous formulation.

10.15. The Committee noted the following network meta-analyses:

- Combe et al. Arthritis Res Ther. 2021;23:119.
- Caporali et al. Expert Rev Clin Immunol. 2021;17:85-99.

10.15.1. The Committee noted both network meta-analyses reported favourable results for the clinical efficacy of subcutaneous infliximab compared to intravenous infliximab in those with rheumatoid arthritis.

10.15.2. The Committee noted the network meta-analyses reported there was an improved or similar benefit to harm ratio for the subcutaneous formulation compared to the intravenous formulation.

10.15.3. The Committee considered that there were some gaps in the data, particularly a lack of comparable clinical efficacy measures, in some analyses.

10.16. The Committee noted the following studies that evaluated the effect of intravenous infliximab compared to subcutaneous formulation in those with inflammatory bowel disease:

- Argüelles-Arias et al. Rev Esp Enferm Dig. 2022;114:118-19.
- Smith et al. J Crohns Colitis. 2022;16:1436-46
- Verma et al. Lancet Gastroenterol Hepatol. 2021;6:88-9
- Duk Ye et al. Lancet. 2019;393:1699-1707.
- Hanzel et al. Aliment Pharmacol Ther. 2021;54:1309-19
- Farkas et al. J Crohns Colitis. 2016;10:1273-78
- Strik et al. Lancet Gastroenterol Hepatol. 2018;3:404-12.
- Gecse et al. J Crohns Colitis. 2016;1:133-40.
- Haifer et al. Med J Aust. 2021;214:128-133.

10.16.1. The Committee noted that the subcutaneous formulation was non-inferior to the intravenous formulation in terms of clinical efficacy and safety in those with inflammatory bowel disease.

10.17. The Committee noted the following studies that evaluated the effect of intravenous infliximab compared to subcutaneous formulation in those with ankylosing spondylitis:

- Vijayan et al. Clin Case Rep. 2022; 10: e05233
- Park et al. Arthritis Res Ther. 2016;18:25.
- Park et al. Ann Rheum Dis. 2013;72:1605-12.
- Park et al. Ann Rheum Dis. 2017;76:346-54.

10.18. The Committee noted the following studies that evaluated the effect of intravenous infliximab compared to subcutaneous formulation in those with a variety of

indications:

- Park et al. Expert Rev Clin Immunol. 2015;11 Suppl 1:S25-31.
- Jørgensen et al. Lancet. 2017;389;2304-16
- Goll et al. J Intern Med. 2019;285:653-69

10.19. The Committee considered there was sufficient and consistent evidence of non-inferiority between subcutaneous and intravenous formulations of infliximab across the indications investigated. The Committee considered that it was reasonable to assume non-inferior clinical efficacy between formulations in other indications where there was no clinical trial data.

10.20. The Committee noted that analysis of the trial data reported that target therapeutic levels would be improved in subcutaneous administration, compared to intravenous administration, in those who weigh up to 150kg. The Committee considered this may be clinically beneficial.

10.21. The Committee noted that paediatric indications have been specifically excluded from the available analyses and that clinicians would likely continue with the intravenous formulation of infliximab.

10.22. The Committee considered that the evidence supporting the benefit of subcutaneous infliximab in rheumatoid arthritis and inflammatory bowel disease was generated from small clinical trials including pharmacokinetic data collection and subsequent pharmacometric modelling. The Committee considered the trials provided high quality evidence of non-inferiority of subcutaneous infliximab, when measured by standard clinical endpoints in these indications, in a predominantly European population.

10.23. The Committee considered that it would be appropriate for both formulations to be funded and available so treatment could be individualised.

10.24. The Committee considered the studies reporting switching between formulations were observational in nature and reported small case series reflecting clinical decisions taken during the COVID pandemic. However, the Committee considered that switching would occur if funded, given the reduced administration time and need for visits to infusion centres.

Suitability

10.25. The Committee considered some may prefer to continue intravenous administration due to needle phobia or not wishing to change their current route of therapy. The Committee noted a 2012 study (Vavricka et al. Inflamm Bowel Dis. 2012 ;18:1523-30) in individuals with Crohn's disease that reported needle phobia was the reason to remain on intravenous infliximab in 10% of people, rather than switching to subcutaneous infliximab.

10.26. The Committee considered there was weak evidence on individual preferences between formulations.

10.27. The Committee noted that there are currently significant resource constraints impacting the delivery of medicines by infusion services in New Zealand.

10.28. The Committee noted that the subcutaneous formulation would enable the pharmaceutical to be administered at home. The Committee noted that most individuals could be trained to self-administer if thought appropriate by a medical practitioner. The Committee noted however that there would be costs associated with

training the individual to administer the pharmaceutical.

10.29. The Committee noted that self-administration will not always be suitable and in cases where there were no other appropriate persons to administer the pharmaceutical, such as caregivers, the administration may need to occur in primary care, which may involve direct costs to the individual.

10.30. The Committee noted that individuals receiving infusions may need to pay for travel and take time off work and have an increased treatment and travel time. Travel time is increased significantly for those who live rurally with large distances to the nearest infusion service.

Cost and savings

10.31. The Committee noted Huynh et al. Patient Prefer Adherence. 2014:8:93-9 that reported in a survey of rheumatology clinics in Denmark approximately 71% of individuals receiving infliximab were currently using subcutaneous infliximab and 77% of new individuals started treatment on the subcutaneous formulation. The Committee considered this is a useful starting point when assessing the impact across indications, however, should more specific estimates of expected uptake be required then Specialist Advisory Committees would need to be engaged to determine the relative usage across indications.

10.32. The Committee noted that those who receive high dose infusions may require the higher 240mg subcutaneous dose to manage their condition. However, the proportion who fall into this category was uncertain.

10.33. The Committee noted the infusion costs Pharmac included in the economic analyses. The Committee considered that the implied cost of an infusion is likely to be a significant underestimate of the current cost, given the demands on infusion centres. Currently, the Committee considered there was likely to be significant variation in infusion costs according to the region of New Zealand; whether the infusion is administered in the public or private sector; and whether individuals required admission to an inpatient facility.

10.34. The Committee considered that a potential method for reflecting the impact of infusion capacity constraints in cost-utility analyses was to assume that a proportion of people in the comparator arm were currently receiving no treatment. The Committee noted that this approach was subject to uncertainty, as it was unclear which individuals were more likely to miss out on treatment as a result of infusion constraints.

10.35. The Committee considered that one of the challenges to estimating the opportunity for improved infusion center capacity from a shift of individuals to subcutaneous infliximab could arise from the current common short infliximab infusion times. Alternative requirements for infusion capacity may well be more complex intravenous regimens with long infusion times. It could not be assumed that there would be a 1:1 individual increase in access to infusion services.

10.36. The Committee considered that the funding of a subcutaneous formulation of infliximab could result in people receiving infliximab earlier in the treatment paradigm for some indications, and that infliximab could therefore displace the use of other biologics. The Committee considered that the extent to which treatment paradigms

may change was uncertain and suggested that it would be useful for Pharmac to seek advice from the relevant Specialist Advisory Committees to inform this.

10.37. The Committee considered there may be an increase in demand for laboratory testing of drug levels to support adequate drug dosing and confirm adherence, most likely in the setting of inadequate clinical response to therapy.

Funding criteria

10.38. The Committee considered that should funding of the subcutaneous formulation be progressed any required amendments to the Special Authority criteria for each indication should be considered by the appropriate Special Advisory Committee.

10.39. The Committee considered that it was important to consider whether the proposed funding criteria allows for similar use of dose escalation, as is currently permitted for the intravenous formulation. The Committee considered that advice should particularly be sought from the Gastrointestinal Advisory Committee to ensure criteria for dose escalation in inflammatory bowel disease are similar across formulations.

Summary for assessment

10.40. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for subcutaneous infliximab if it were to be funded in New Zealand for all currently funded intravenous infliximab indications. The Committee note that the comparator for this assessment may be subject to change, as further information is received from relevant specialist groups. 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.

Population	Same population as is eligible for intravenous infliximab. Likely that this will include some people switching from other biologics, as well as people receiving the intravenous formulation.
Intervention	Infliximab subcutaneous at 120 mg once every 2 weeks Some individuals may require escalation to 240mg every two weeks
Comparator(s) (NZ context)	Principal comparator is intravenous infliximab Likely that some people may take subcutaneous infliximab as an alternative to other biologics (e.g. adalimumab). Examples include: - **Crohn's disease and ulcerative colitis** – subcutaneous infliximab may displace adalimumab or other biologics - **Psoriasis** – subcutaneous infliximab may displace adalimumab, etanercept, or secukinumab - **Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis** – subcutaneous infliximab may displace other second-line anti-TNFs (e.g. etanercept) Proportion of people switching from other biologics to intravenous infliximab likely to differ by indication - Advice should be sought from relevant Specialist Advisory Committees on this input

Outcome(s)	**Infliximab subcutaneous versus intravenous administration** Subcutaneous infliximab non-inferior to intravenous in rheumatoid arthritis, based on DAS-28-CRP scores at week 22 (Westhovens et al, Rheumatology (Oxford). 2021; 60: 2277-87). - Based on the evidence in rheumatoid arthritis, efficacy of subcutaneous infliximab assumed to be similar to intravenous across funded indications - Principal benefit of subcutaneous infliximab would be suitability benefit (including health system benefits associated with this) **Infliximab subcutaneous versus other biologics potentially displaced** - The change in treatment outcomes associated with this is likely to differ by treatment displaced, and indication of interest.

Table definitions:

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

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

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

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

11. Ofatumumab for relapsing remitting multiple sclerosis

Application

11.1. The Committee reviewed the application from Novartis for the use of ofatumumab (Kesimpta) for the treatment of relapsing remitting multiple sclerosis (RRMS).

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 ofatumumab be listed only if **cost-neutral** to ocrelizumab (at an individual level and accounting for up to date infusion costs), subject to the current Special Authority criteria for treatments used in RRMS.

11.4. In making this recommendation, the Committee considered that ofatumumab has comparable safety and efficacy to currently funded monoclonal antibodies for multiple sclerosis (MS) such as ocrelizumab. The Committee considered that the key Factor for Consideration was Suitability given that the additional benefit of ofatumumab over funded alternatives is its mode of delivery as a subcutaneous injection.

Discussion

Māori impact

11.5. The Committee discussed the impact of funding ofatumumab for the treatment of RRMS on Māori health areas of focus and Māori health outcomes. The Committee noted that MS is not one of the Hauora Arotahi Māori health areas of focus, and that the prevalence of MS in Māori has been reported to be appreciably lower than non-

Māori (Pearson et al. Mult Scler. 2014;20:1892-5).

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

11.6. The Committee discussed the impact of funding ofatumumab for the treatment of RRMS on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted that Pacific peoples are less likely to be affected by MS given that the disease predominantly affects those of Northern European ancestry (Taylor et al Mult Scler. 2010;16:1422-31).

Health need

11.7. The Committee noted that MS predominantly affects Caucasian people; that a north to south latitudinal gradient is associated with an increase in prevalence of MS in the New Zealand total population; and that for many people, RRMS ultimately becomes secondary progressive MS (SPMS). The Committee considered that Pharmac is aware of the health need of people with RRMS and their families and whānau, noting the advice provided in 2018 for ocrelizumab for RRMS, and considered there was no new advice to be provided about health needs at this time.

Health benefit

11.8. The Committee noted that ofatumumab is a fully human anti-CD20 monoclonal antibody that is given at a dose of 20 mg as a weekly subcutaneous injection for three weeks and then monthly. The Committee considered that the first injection would be given in a medical clinic and subsequent doses would be self-administered at home.

11.9. The Committee considered that no B-cell monitoring would be required alongside treatment with ofatumumab given the low dose used for RRMS and the absence of safety concerns relating to B-cell levels in the large clinical trial populations. The Committee noted that other anti-CD20 monoclonal antibodies such as ocrelizumab can cause hepatitis B (HBV) reactivation in those with prior HBV infection, and that people commencing treatment with ocrelizumab are tested for HBV prior. The Committee considered it was reasonable for Pharmac to assume that HBV serology tests and vaccination or treatment for HBV, as applicable, would be required with ofatumumab.

11.10. The Committee noted that ofatumumab was recommended for the treatment of RRMS by several international funding agencies in 2021 who considered it to be superior to teriflunomide (PBAC, Australia and CADTH-CDEC, Canada); superior to other disease-modifying therapies (DMTs) (SMC, Scotland) and superior to a number of DMTs and equivalent to intravenous (IV) natalizumab and ocrelizumab (NICE, England and Wales). The Committee considered that the assumptions in the NICE CUA were likely applicable to the New Zealand context.

11.11. The Committee noted the evidence came from two key clinical trials, ASCLEPIOS I and ASCLEPIOS II, which were identical randomised (1:1), controlled, double-blind, double-dummy, multicentre phase 3 trials that were conducted concurrently (Hauser et al. N Engl J Med. 2020;383:546-57). The trials included a total of 1,882 people aged 18-55 years with MS with a relapsing–remitting course (~94%) or a secondary progressive course (~6%), disease activity, and Expanded Disability Status Scale (EDSS) score of 0 to 5.5. Participants had at least one relapse, or one lesion on MRI,

in the year prior, or at least 2 relapses in the two years prior. About 40% of participants were treatment naïve and the mean EDSS score was about three. Participants received ofatumumab SC (20 mg weekly loading doses for three weeks, then 20 mg every four weeks) or oral teriflunomide (14 mg once daily) for up to 30 months on treatment.

11.11.1. The Committee noted that the rationale for teriflunomide, which has a different mechanism of action, as comparator was unexplained, but considered that this was likely chosen so that the trial could demonstrate a superiority benefit (as opposed to noninferiority) with ofatumumab. The Committee noted that the authors reported in detail the extent of Novartis involvement in the trial and the rationale for this.

11.11.2. The Committee noted that the primary endpoint of annualised relapse rate (ARR) was reported after median follow-up of 1.6 years, with about 30% of participants on medication for approximately two years. The Committee noted that the ARR in ASCLEPIOS I was 0.11 with ofatumumab and 0.22 with teriflunomide (difference, −0.11; 95% confidence interval [CI], −0.16 to −0.06; *P*<0.001) and ARR in ASCLEPIOS II was 0.10 with ofatumumab and 0.25 with teriflunomide (difference, −0.15; 95% CI, −0.20 to −0.09; *P*<0.001). The Committee noted that the authors concluded both medicines reduced relapse rates, but that ofatumumab was better than teriflunomide.

11.11.3. The Committee noted that confirmed disability worsening (CDW) using pooled data from the two trials was 10.9% with ofatumumab and 15.0% with teriflunomide at three months (hazard ratio, HR: 0.66; 95% CI, 0.50 to 0.86; *P* =0.002) and at six months CDW was 8.1% with ofatumumab and 12.0% with teriflunomide (HR 0.68; *P*=0.01). The Committee noted that there was no difference in confirmed disability improvement at six months.

11.11.4. The Committee noted that the radiological endpoints in the ASCLEPIOS trials and considered that while they were clinically relevant, relapse and disability endpoints would be most important for people with MS. The Committee noted that adverse events were similar between treatment groups in the trials, however, considered that the greater incidence of alopecia with teriflunomide (occurring in about 15%) would likely be quite important to people with MS.

11.12. The Committee noted a post-hoc analysis of 615 participants who were treatment naïve at entry into ASCLEPIOS I and II (Gärtner et al. Mult Scler. 2022;28:1562-75). The Committee noted that in this subgroup, the ARR was reduced by 50% with ofatumumab compared to teriflunomide (0.09 ofatumumab vs. 0.18 teriflunomide; rate ratio 0.50 [95% CI: 0.33, 0.74]; *P*<0.001); the six-month CDW was delayed by 46% versus teriflunomide (HR 0.54 [95% CI: 0.30, 0.98]; *P*=0.044); and six-month progression independent of relapse activity was delayed by 56% with ofatumumab (HR 0.44 [95% CI: 0.20, 1.00]; *P*=0.049). The Committee considered that the safety profile was similar to that in the overall populations of ASCLEPIOS I and II.

11.13. The Committee noted evidence from ALITHIOS; a phase IIIb, open-label, long term safety study of 1,969 participants from ASCLEPIOS I and II, or the phase II trials APLIOS or APOLITOS (Hauser et al. Mult Scler. 2022; 28: 1576–90). The Committee noted that no new safety findings were reported after median treatment duration of about three years.

11.14. The Committee noted evidence from the following indirect treatment comparisons (meta-analyses) in the absence of other head-to-head comparisons:

- Samjoo et al. J Comp Eff Res 2020; 9(18): 1255-74
- Samjoo et al. Mult Scler Relat Disord. 2022;66:104031
- Chen et al. J Am Pharm Assoc. 2022;63:8-22
- Hennessey et al. Mult Scler Relat Dis. 2022;64:103908

11.15. The Committee noted that Samjoo et al. (2020) confirmed the ASCLEPIOS trial findings based on 30 predominantly randomised-controlled studies. The Committee noted that the authors indicated that ofatumumab SC may be as effective as other highly efficacious monoclonal antibody DMTs in this setting and that ofatumumab is either superior to, or not statistically different to, all other DMTs in terms of relapse rate and disability progression. The Committee noted that the authors reported a low risk of bias, and that the heterogeneity of studies did not materially impact results.

11.16. The Committee noted that Samjoo et al. (2022) simulated treatment comparisons using individual patient data from ASCLEPIOS I/II (ofatumumab) and publicly available summary-level data from OPERA I/II (ocrelizumab) to assess the comparative efficacy as three- and six-month confirmed disease progression (CDP) and ARR. The Committee noted that the authors adjusted for differences in baseline characteristics and reported that the ARR statistically significantly favoured ofatumumab and considered that this was a different conclusion to that reported by other available evidence.

11.17. The Committee noted evidence from forty-five randomised controlled trials with a total of 30,720 participants that were included in pairwise and indirect comparison network meta-analyses investigating safety and efficacy of all DMTs for relapsing MS (Chen et al. 2022). The authors concluded that ofatumumab was efficacious, but less so than alemtuzumab or natalizumab, in terms of ARR. The Committee noted that the authors reported 12-week CDP with ofatumumab was better than that with other DMTs, however, other monoclonal antibodies were not analysed. The Committee noted that the authors also considered that later assessment (eg 24 weeks) would better capture treatment effects.

11.18. The Committee noted an indirect comparison network meta-analysis of 21 studies dating back to 1987, many of which were included in the Chen et al. meta-analysis (Liu et al. Autoimmun Rev. 2021;20:102826). The Committee noted that the authors reported that the ARR for most DMTs was significantly lower compared with placebo; that ocrelizumab and ofatumumab had the largest reduction in risk of CDP at three months; and that ofatumumab and natalizumab showed the best efficacy and compliance based on surface under the cumulative ranking curve (SUCRA).

11.19. The Committee noted another indirect comparison network meta-analysis investigating the comparative efficacy and safety of anti-CD20 monoclonal antibodies for RRMS (Asha et al. IBRO Neurosci Rep. 2021;11:103-11). The Committee noted that the authors included the ASCLEPIOS trials although they did not involve the nominated common comparator (interferon) and they reported results that were not the aim of the study.

11.20. The Committee noted the following additional evidence identified by Pharmac staff:

- Śladowska et al. Neurol Sci. 2022;43:5479-500
- Baharnoori et al. Pharmacoecon Open. 2022;6:859-70

- Simpson et al.Curr Treat Options Neurol. 2021;23:19
- Montgomery et al. J Med Econ. 2023;26:139-48
- von Essen et al. Neurol Neuroimmunol Neuroinflamm. 2022;9:e200004

11.21. The Committee considered that the indirect evidence for ofatumumab was strong based on the key phase III trials. However, the Committee noted that direct comparison with other monoclonal antibodies (mAbs) used for the treatment of RRMS such as ocrelizumab, which are the most relevant comparators in terms of efficacy, was absent. Members considered that the length of trial follow-up out to about three years was short relative to the many years it may take to change EDSS score states. The Committee considered that ofatumumab offered no additional health benefits over currently funded mAbs for RRMS. The Committee considered that ofatumumab was similar to other mAbs for the treatment of RRMS and likely superior to other DMTs for RRMS for relapse rate and disability worsening.

Suitability

11.22. The Committee considered that the main benefit of ofatumumab over currently funded MABs for MS, which require infusion, is its formulation as a subcutaneous injection. The Committee considered that ofatumumab can be self-administered via a prefilled injection pen, although some people may not wish to self-inject.

Cost and savings

11.23. The Committee noted that ofatumumab would be associated with a reduction in chair time at infusion services and associated costs where it displaces IV treatment. Members considered that currently natalizumab and in some cases, ocrelizumab, is given on a six-weekly dosing schedule instead of four-weekly with total chair time per infusion of 30-60 minutes for natalizumab and two hours for ocrelizumab. Members were not aware of any extended dosing occurring in practice with ofatumumab.

11.24. The Committee considered that actual displacement rates for natalizumab and for oral MS treatments would be higher than the supplier estimated. Members considered that JC virus (JCV) positive people receiving ocrelizumab who need a higher efficacy treatment would likely switch to ofatumumab instead of natalizumab due to the significant risk of progressive multifocal leukoencephalopathy (PML) with the latter; JCV negative people with MS would likely receive natalizumab which is considered safe and effective in that subgroup. Members considered that very few people with MS receive older injectable medicines (ie interferon beta-1 alpha, interferon beta-1-beta, and glatiramer acetate) and as those people would be receiving a long-term response to treatment, it is unlikely they would switch to a higher efficacy treatment like ofatumumab.

11.25. The Committee considered that ofatumumab should be listed only if cost-neutral to ocrelizumab (at an individual level) as the most relevant mAb comparator, and that Pharmac should use up to date infusion costs when taking this into account.

Funding criteria

11.26. The Committee noted that the same funding criteria was in place for all MS treatments used in RRMS and considered that there was no reason to apply different criteria to ofatumumab for RRMS.

Summary for assessment

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

Population	People with relapsing-remitting multiple sclerosis with an EDSS score of 0-6, who meet the 2017 McDonald criteria
Intervention	Ofatumumab 20 mg subcutaneous injection administered at weeks 0, 1, and 2 followed by monthly dosing starting at week 4. Treatment is ceased if EDSS score progresses above EDSS 6.
Comparator(s)	Ocrelizumab (at an individual level). (NB. For the purposes of this assessment, a weighted average of currently funded RRMS treatments will also be estimated for both costs and treatment efficacy in the overall population with RRMS.)
Outcome(s)	• Reduced annualised relapse rates (ARR) compared to moderate-efficacy MS treatments and similar ARR compared to ocrelizumab and natalizumab, as demonstrated in the ASCLEPIOS trials and the Network Meta Analysis (NMA) (Samjoo et al. J Comp Eff Res 2020; 9(18): 1255-74) • Reduced rates of confirmed disability worsening at 3/6 months (CDW-3 or CDW-6)) compared to moderate-efficacy MS treatments and similar CDW-3/CDW-6 compared to ocrelizumab and natalizumab, as demonstrated in the ASCLEPIOS trials and NMA • Improved health-related quality of life due to lower rates of ARR and CDW • Lower rates of mortality associated with more time spent in lower EDSS states Savings to the wider health system due to more time spent in lower EDSS states and reduced burden on infusion services due to displacement of ocrelizumab and natalizumab

Table definitions:

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

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

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

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