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 16 November & 17 November 2023

1. Present:

PTAC members:
Jane Thomas (Chair)
Rhiannon Braund (Deputy Chair)
Alan Fraser
Brian Anderson
Helen Evans
James Le Fevre
John Mottershead
Liza Lack
Matthew Dawes
Matthew Strother
Robyn Manuel
Simon Wynn Thomas
Stephen Munn

PTAC Members in attendance for parts of the meeting:
Elizabeth Dennett

Apologies:
Bruce King
Lisa Stamp

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

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

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

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

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

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

3. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
7.3	Upadacitinib for the first line treatment of Crohn's disease	High Priority
7.4	Upadacitinib for the second line treatment of Crohn's disease	High Priority
7.32	Secukinumab for the first line biologic treatment of ankylosing spondylitis	Decline
8.3	Budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler for maintenance treatment to prevent exacerbations, relieve symptoms in adults with moderate to very severe COPD	Cost Neutral
9.3	Guselkumab in the first-line biologic treatment of psoriatic arthritis	Decline
9.4	Guselkumab in the second-line biologic treatment of psoriatic arthritis	Cost Neutral
10.1	Cladribine for the treatment of relapsing-remitting multiple sclerosis	Cost Neutral
11.1	Memantine for the treatment of dementia	Decline
12.3	Belimumab for the treatment of active lupus nephritis	High Priority

4. Record of PTAC meeting held 17 August & 18 August 2023

4.1. The Committee reviewed the record of the PTAC meeting held on 17 & 18 August 2023.

4.2. The Committee accepted the record.

5. Pharmac Update

5.1. The Committee noted the Pharmac Update.

6. Specialist Advisory Committee Record

17 March 2023 Nephrology Meeting Record

6.1. PTAC reviewed the record of the Nephrology Advisory Committee held on the 17 March 2023

6.2. PTAC noted the Nephrology Advisory Committee's discussion regarding indomethacin and its current unavailability in the community setting due to there being no Medsafe approved product available.

6.3. PTAC noted the other items discussed at the Nephrology Advisory Committee's meeting held on 17 March 2023.

7 March 2023 Rare Disorders Meeting Record

6.4. PTAC reviewed the record of the Rare Disorders Advisory Group Meeting held on the 7 March 2023.

6.5. PTAC noted the record and acknowledged the contribution of patients with lived experience at this meeting.

11 July 2023 Mental Health DHD renewal criteria Meeting Record and update

6.6. PTAC reviewed the record of the Mental Health Advisory Committee held on the 11 July 2023

6.7. PTAC noted the Mental Health Advisory Committee's discussion on general practice managing ongoing stimulant treatment for attention deficit hyperactivity disorder (ADHD). PTAC considered that general practice could manage this effectively, however prescriber education would be important. Additionally, PTAC considered that general practice would benefit from an established network with specialist services that would support appropriate and sustainable review of ongoing ADHD stimulant treatment.

6.8. PTAC noted that the Mental Health Advisory Committee's discussion was focused on the renewal criteria for stimulant treatments and not access considerations related to initiating stimulant treatment for ADHD. PTAC considered there are less concerns for access to stimulant treatment for children and adolescents relative to adults with ADHD. PTAC considered currently there is not adequate funding for general practice to support lengthier appointments that would be required for more rigorous assessment and diagnosis of ADHD.

28 April 2023 CTAC record

6.9. PTAC reviewed the records of the Cancer Treatments Advisory Committee (CTAC) held on 28 April 2023.

6.10. PTAC noted the records.

30 May 2023 COVID-19 Treatments Advisory Group Meeting Record – Long COVID; COVID-19 outcomes in Disability Support Services (DSS) recipients

6.11. PTAC reviewed parts of the record of the COVID-19 Treatments Advisory Group held on 30 May 28 April 2023, being those relating to Long COVID and to COVID-19 outcomes in Disability Support Services (DSS) recipients.

6.12. PTAC noted the records of these items.

7. Correspondence & Matters Arising

Upadacitinib for the first and/or second line treatment of Crohn's disease

Application

7.1. The Advisory Committee reviewed upadacitinib for the first and/or second line treatment of Crohn's disease.

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

Recommendation

7.3. The Advisory Committee **recommended** that upadacitinib for the first line treatment of Crohn's disease be funded with a **high priority** subject to the following Special Authority criteria:

UPADACITINIB

Initiation –Crohn's disease- adult

Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. Individual has active Crohn's disease and
2. Any of the following:
   - 2.1. Patient has Crohn's disease active index (CDAI) score of greater than or equal to 300; or HBI score greater than or equal to 10; or
   - 2.2. Patient has extensive small intestine disease affecting more than 50cm of the small intestine; or
   - 2.3. Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
   - 2.4. Patient has an ileostomy or colostomy and has intestinal inflammation; and
3. Any of the following:
   - 3.1. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   - 3.2. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   - 3.3. Immunomodulators and corticosteroids are contraindicated.

Renewal –Crohn's disease – adult

Applications only from any relevant practitioner. Approvals valid for 2 years.

All of the following:

1. Either
   - 1.1. CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on biological therapy; or HBI score has reduced by 3 points from when patient was initiated on biological therapy or
   - 1.2. CDAI score is 150 or less, or HBI is 4 or less; or
   - 1.3. The patient has experienced an adequate response to treatment, but CDAI score cannot be assessed and
2. Upadacitinib to be administered at a dose no greater than 30mg daily.

Initiation –Crohn's disease- children

Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. Individual has active Crohn's disease and
2. Any of the following:
   - 2.1. Patient has Paediatric Crohn's Disease Active Index (PCDAI) score of greater than or equal to 30;
   - 2.2. Patient has extensive small intestine disease and
3. Any of the following:
   - 3.1. Patient has had an initial approval for prior biologic therapy and has experienced intolerable side effects or insufficient benefit to meet renewal criteria (unless contraindicated) or
   - 3.2. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   - 3.3. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   - 3.4. Immunomodulators and corticosteroids are contraindicated; and

Renewal –Crohn's disease – children

Applications only from any relevant practitioner. Approvals valid for 2 years.

All of the following:

1. Either
   - 1.1. PCDAI score has reduced by 10 points from when the patient was initiated on biological therapy; or
   - 1.2. PCDAI score is 15 or less or
   - 1.3. The patient has experienced an adequate response to treatment, but PCDAI score cannot be assessed and
2. Upadacitinib to be administered at a dose no greater than 30mg daily.

7.4. The Advisory Committee **recommended** that upadacitinib for the second line treatment of Crohn's disease be funded with a **high priority** subject to the following Special Authority criteria:

UPADACITINIB

Initiation –Crohn's disease- adult

Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. Individual has active Crohn's disease and
2. Patient has had an initial approval for prior biologic therapy and has experienced intolerable side effects or insufficient benefit to meet renewal criteria (unless contraindicated)

Renewal –Crohn's disease – adult

Applications only from any relevant practitioner. Approvals valid for 2 years.

All of the following:

1. Either
   - 1.1. CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on biological therapy; or HBI score has reduced by 3 points from when patient was initiated on biological therapy or
   - 1.2. CDAI score is 150 or less, or HBI is 4 or less; or
   - 1.3. The patient has experienced an adequate response to treatment, but CDAI score cannot be assessed and
2. Upadacitinib to be administered at a dose no greater than 30mg daily.

Initiation –Crohn's disease- children

Applications only from a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. Individual has active Crohn's disease and
2. Patient has had an initial approval for prior biologic therapy and has experienced intolerable side effects or insufficient benefit to meet renewal criteria (unless contraindicated)

Renewal –Crohn's disease – children

Applications only from any relevant practitioner. Approvals valid for 2 years.

All of the following:

1. Either
   - 1.1. PCDAI score has reduced by 10 points from when the patient was initiated on biological therapy; or
   - 1.2. PCDAI score is 15 or less or
   - 1.3. The patient has experienced an adequate response to treatment, but PCDAI score cannot be assessed and
2. Upadacitinib to be administered at a dose no greater than 30mg daily.

7.5. The Committee considered the following in making its recommendations:

- Recent evidence and the results of phase 3 trials in this setting
- The increased suitability of the treatment compared to funded infusion-based treatments.
- The health equity for Māori and those in rural areas, with the oral formulation enabling greater access to treatment.

7.6. The Committee requested Pharmac review the current Special Authority criteria for inflammatory bowel disease biologic/ targeted treatments, regarding the severity of disease included with the current Crohn's disease active index and Harvey-Bradshaw Index scoring, with a view to decreasing the scoring to match clinical trial inclusion criteria. The Committee also noted that the current Harvey Bradshaw Index score maps onto a higher level of disease severity than the current Crohn's disease active index score.

Discussion

Māori impact

7.7. The Committee discussed the impact of funding upadacitinib for the first and/or second line biologic/ targeted treatment of Crohn's disease on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes. The Committee noted Crohn's disease is a Hauora Arotahi. The Committee noted a recent study performed in the Waikato region of New Zealand that reported a higher rate of prevalence in Māori, than reported in a 2005 study in the Canterbury region, of 61.4 per 100,000 compared to 41.6 per 100,000 respectively (Seleq et al. Intern Med J, 2023, pre print, Gearry et al. Inflamm Bowel Dis 2006;12:936-43).The Committee noted the oral formulation would allow for greater treatment access compared with other funded intravenous treatment options.

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

7.8. The Committee discussed the impact of funding upadacitinib on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee considered Pacific peoples and individuals of South Asian ethnicity present younger, with an increasing proportion presenting between the ages of 0-24 years of age (Seleq et al. 2023 pre print, Gearry et al. 2006). The Committee considered people in rural areas may have reduced access to infusion services for currently funded treatments. The Committee noted the oral formulation would allow for greater treatment access compared with other funded intravenous treatment options, for this population group as well as for individuals with a phobia of needles.

Background

7.9. The Committee noted it had previously considered upadacitinib for inflammatory bowel disease (IBD) and had recommended that upadacitinib be listed for the treatment of ulcerative colitis with a **medium priority** for **first-line** biologic/ targeted treatment, and **high priority** for **second-line** biologic/ targeted treatment (PTAC, May 2023).

7.10. The Committee noted it had, however, **deferred** making recommendations for upadacitinib for the treatment of Crohn's disease until further evidence and the results of phase 3 trials in this setting are published (PTAC, May 2023).

Health need

7.11. In addition to its previous considerations of Crohn's disease, the Committee noted Seleq et al. 2023 reported an increase in the prevalence and incidence of IBD in New Zealand between 2010 and 2019.

7.12. The Committee noted that whilst Crohn's disease does not disproportionally affect Māori or Pacific peoples, the prevalence in both population groups has been increasing over time. The Committee noted Seleq et al. 2023 reported the prevalence of IBD in Māori, in the Waikato region of New Zealand, was higher than previously reported in the Canterbury region (Gearry et al. Inflamm Bowel Dis 2006;12:936-43). The 2023 study reported a prevalence in Māori of 61.4 per 100,000 compared to 41.6 per 100,000 reported previously in 2006.

7.13. The Committee considered there was an approximate doubling in the number of people with Crohn's disease aged 0 to 24 years. The Committee also noted that there were increasing numbers of Māori and Pacific peoples presenting in that age range. The Committee noted that people of South Asian ethnicity were also more likely to present earlier (Rajasekaran et al. J Pediatr Gastroenterol Nutr. 2023;76:749-55).

Health benefit

7.14. The Committee noted it had reviewed evidence of health benefit for upadacitinib in Crohn's disease in May 2023, and that results of phase 3 trials in this setting had since been published.

7.15. The Committee noted Loftus et al. N Engl J Med 2023; 388:1966-80, a phase 3 randomised, double blind, placebo controlled study, that included 526 and 502 participants from the U-EXCEL and U-ENDURE trials respectively. The study included a 12-week induction period, followed by a 52-week maintenance phase. The Committee noted the following trial results:

- Clinical remission in U-EXCEL, was 49.5% with 45 mg upadacitinib vs. 29.1% placebo; in U-EXCEED, 38.9% vs. 21.1% and an endoscopic response in U-EXCEL, 45.5% vs. 13.1%; in U-EXCEED, 34.6% vs. 3.5% (45mg upadacitinib vs placebo respectively, P<0.001 for all comparisons).

- At week 52 in U-ENDURE, a higher percentage had clinical remission with 15 mg upadacitinib (37.3%) or 30mg upadacitinib (47.6%) than with placebo (15.1%), and a higher percentage had an endoscopic response with 15 mg upadacitinib (27.6%) or 30 mg upadacitinib (40.1%) than with placebo (7.3%) (P<0.001 for all comparisons).

- Herpes zoster infections occurred more frequently in the 45 mg and 30 mg upadacitinib groups vs placebo. Hepatic disorders and neutropenia were more frequent in the 30 mg upadacitinib group vs other maintenance groups. Gastrointestinal perforations developed in n=4 with 45 mg upadacitinib and in n=1 each who received 30 mg or 15 mg upadacitinib.

- The Committee noted that the inclusion criteria for the trial population in the U-EXCEED and U-EXCEL studies were broadly comparable to the New Zealand population, however the trial cohort was likely had less severe disease than those currently funded for biologic treatment in New Zealand. The Committee noted prior treatments in the trial included certolizumab, which is not funded in New Zealand.

- The Committee noted that both trials included a cross over in treatment, which can limit interpretation of results. The Committee noted those who had placebo treatment, and individuals whose disease did not respond in the induction study, were eligible for 45 mg upadacitinib treatment in the extended treatment period. The Committee noted that both extended treatment periods randomised only those who had responded to treatment to the maintenance phase of the trial. The Committee noted the trial population was therefore more likely to have a higher success rate for the maintenance population compared to the general population.

- The Committee noted in the U-ENDURE maintenance phase of the trial, the group that received 30 mg upadacitinib were less likely to receive rescue therapy compared to 15 mg or placebo group, with 25.6% receiving rescue treatment compared to 34.3% and 61.8% respectively. The 30 mg group were also more likely to complete blinded treatment, with 62.5% completing, compared to 52.1% and 27.3% respectively. The Committee considered the maintenance study results might underestimate the efficacy of 30 mg upadacitinib treatment based on the need to use a rescue treatment.

- The Committee considered at 12 and 52 weeks, for both the U-EXCEL and U-EXCEED trials, the number of participants in CDAI clinical remission, and that achieved endoscopic response, were broadly similar or better than those reported for trials with vedolizumab or ustekinumab. The Committee noted that there were differences in timelines, endpoints, and statistical approaches between the trials which can affect comparing the results.

- The Committee noted that the majority of people that achieved clinical remission with upadacitinib treatment remained on maintenance treatment over the course of 52 weeks, with a low discontinuation rate.

- The Committee noted the number of adverse events, and serious adverse events, for upadacitinib at week 12 in the U-EXCEL and U-EXCEED trials were slightly higher than ustekinumab.

- The Committee noted in the maintenance trial, at 52 weeks, adverse events were reported as “number of patients (events per 100 persons per year)”. The Committee considered it was challenging to compare this to the number of adverse events for ustekinemab or vedolizumab which were reported as the “number of adverse events (percentage)”.

7.16. The Committee noted the endpoints of CDAI and Simple Endoscopic Score for Crohn's Disease (SES-CD) were common endpoints used in IBD clinical trials.

- The Committee noted that whilst neither endpoint was fully validated, both had been used extensively since the early 1980’s. The Committee noted that CDAI had been used extensively in the registration of other IBD therapeutics, and considered reduction in CDAI score does seem to predict a biologic response in practice.

7.17. The Committee noted a Cochrane review of endoscopic scoring that reported that whilst inter-rater reliability of SES-CD scoring was high between two reviewers in the development study for SES-CD, the two reviewers were in the same room, and therefore there was the possibility for bias (Khanna et al. Cochrane Database Syst Rev. 2016;2016:CD010642).

7.18. The Committee considered Harvey-Bradshaw Index (HBI) scoring was more likely to be used in practice, due to being shorter to complete than CDAI scoring.

7.19. The Committee noted Collen et al. Inflamm Bowel Dis. 2023;29:1175-76, an observational case study that reported the use of upadacitinib in one child with IBD. The Committee noted the sparsity of evidence for use of biologic or targeted treatments in children with IBD. The Committee noted there were ongoing clinical trials in paediatric populations. The Committee noted upadacitinib is recommended for use in children and is used in clinical practice in other countries. The Committee considered sparsity of evidence was not a contraindication to use, and the oral formulation has suitability advantages in children.

7.20. The Committee noted Barberio et al, Gut. 2023;72:264-74, an indirect comparison network meta-analysis that compared upadacitinib with other biologic and targeted therapeutics for Crohn’s disease. The Committee noted the study reported that upadacitinib, relative to other treatments, have a generally lower rate of failure to maintain clinical remission or response in a second-line setting. The Committee considered that the results of this indirect comparison suggested a trend towards upadacitinib being superior to other biologics in a second-line setting, however considered that the magnitude and certainty of this was unclear, given the differences across trials. The Committee considered that the meta-analysis did not allow for comparisons between upadacitinib and other biologics in a first-line setting, and therefore that there was insufficient evidence to suggest there was a treatment benefit first-line.

7.21. The Committee also noted Doecke et al. Aliment Pharmacol Ther. 2017;45:542-52, an observational New Zealand and Australian cohort study that reported infliximab and adalimumab having similar maintenance of response in second line treatment.

Suitability

7.22. The Committee noted that upadacitinib is administered as an oral treatment, which would reduce the need for individuals to attend infusion centres compared with other funded treatments.

7.23. The Committee considered that a reduction in infusion administration may particularly benefit younger individuals, who may currently require peripherally inserted central catheter (PICC) lines due to loss of venous access over time, and may need to leave work and/or school to attend appointments.

7.24. The Committee considered the use of an oral formulation would also be of benefit to individuals with a needle phobia.

7.25. The Committee considered that for some younger individuals, pill burden can result in reduced adherence to treatment, and that for some individuals, infusions or subcutaneous injections may still be more appropriate due to the benefits gained from treatment adherence.

Cost and savings

7.26. The Committee considered that persistence rates in New Zealand may be higher in practice than in clinical trials, due to individuals feeling improvement in symptoms are sufficient in comparison to baseline levels.

Funding criteria

7.27. The Committee noted that the current Special Authority criteria HBI index included those who had more severe disease and were more stringent than the clinical trial criteria. The Committee also noted that the current HBI score maps onto a higher level of disease severity than the current CDAI score.

7.28. The Committee requested Pharmac review the current Special Authority criteria for IBD biologic/ targeted treatments, regarding the severity of disease included with the current CDAI and HBI scoring, with a view to decreasing the scoring to match clinical trial inclusion criteria. The Committee also noted that the current HBI score maps onto a higher level of disease severity than the current CDAI score.

Summary for assessment

7.29. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for Crohn's 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 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 severe Crohn's disease who have experienced inadequate benefit from prior conventional and/or biologic therapy. Individuals may receive upadacitinib as a first line treatment, or after failure of a biologic agent. Based on limited evidence, assumes: - 30% of people may receive upadacitinib as a first-line agent (taking into account clinician familiarity with adalimumab and other first-line agents) - 70% of people receive upadacitinib after prior biologic failure
Intervention	Upadacitinib, 45 mg once-daily for first 12 weeks, followed by 15 mg or 30 mg daily thereafter. Proportion of people receiving each of 15 mg and 30 mg dosage for maintenance is uncertain, likely to be >80% based on previous PTAC advice in May 2023 in the context of UC.
Comparator(s)	Funded biologic therapy. First-line, comparator agents estimated to be: - adalimumab (~85%) - vedolizumab (~5%) - infliximab (~10%) Note that in children, infliximab is likely to be the first-line comparator, with other agents less likely. Second-line, comparator agents estimated to be: - ustekinumab (~70%) - vedolizumab (~30%) No material difference is expected in second-line comparator according to age. For third-line and fourth-line therapy, it is assumed people receive vedolizumab or infliximab.
Outcome(s)	**Outcomes vs no biologic treatment** Improved rates of clinical response and remission, based on the results reported in Loftus Jr et al. N Engl J Med 2023;388: 1966-80. - Improved rates of clinical response and remission assumed to be associated with lower health system costs associated with severe Crohn's disease. **Outcomes vs funded comparators (mainly adalimumab first-line and ustekinumab / vedolizumab second-line)** Uncertain magnitude of benefit compared to funded biologic treatments, in either a first or second-line setting. *First-line* - Assumed to be similarly effective to anti-TNFs in a first-line setting, based on no evidence of superiority. - Rates of improvement numerically similar to those reported for infliximab and adalimumab (see Colombel et al. Gastroenterol 2007;132: 52-65; Hanauer et al. Lancet 2002;359: 1541-9). *Second-line* - Trend towards superiority compared to currently funded biologics, based on the network meta-analysis by Barberio et al. Gut 2023;72: 264-74. Magnitude of benefit uncertain. Note that in both listing scenarios, upadacitinib would offer an additional line of treatment and therefore offer additional health benefit compared to no biologic treatment.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Secukinumab for the treatment of ankylosing spondylitis, 1st biologic line

Application

7.30. The Advisory Committee reviewed the application for secukinumab for the treatment of ankylosing spondylitis.

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

Recommendation

7.32. The Advisory Committee **recommended** that secukinumab for the first line biologic treatment of ankylosing spondylitis (AS) be **declined** for funding.

7.33. The Advisory Committee considered the following in making its recommendation:

- The lack of evidence to suggest clinical advantage over existing funded treatments.
- The increased cost associated with secukinumab, compared to comparator treatments.
- Secukinumab is currently funded as a second line biologic treatment for AS
- The lack of peer reviewed published evidence since the Committee last reviewed the application in February 2018, however noted it would be open to review if peer reviewed published evidence of clinical benefit over existing funded treatment becomes available.

Discussion

Māori impact

7.34. The Committee discussed the impact of funding secukinumab for the treatment of AS on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes. The Committee noted AS is not a Hauora Arotahi. The Committee considered that Māori are not overrepresented in individuals with AS, and the HLA-B27 allele which is correlated with developing AS is less common in Māori than non-Māori (6.5% compared to 9.2% respectively). However, the Committee considered it unclear how health beliefs and healthcare access affect the identification and diagnosis of AS and subsequent access to biologic treatments.

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

7.35. The Committee discussed the impact of funding secukinumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee considered it is unclear how health beliefs and healthcare access for Pacific peoples, low decile, mobile and rural populations affect diagnosis rates for AS and access to biologic treatments. The Committee considered that Māori, and people with more physical jobs may be less likely to present to healthcare professionals, and therefore less likely to be diagnosed, treated, and access biologic treatments.

Background

7.36. The Committee reviewed this application in February 2018 and deferred making a recommendation, pending publication of the results of the SURPASS trial of secukinumab as first-line biologic treatment in AS comparing against an adalimumab biosimilar. Secukinumab has been funded as a second line biologic treatment for AS since 2021.

Health need

7.37. The Committee noted it had discussed the health need of those with AS in May 2022, and noted the Rheumatology Advisory Committee record regarding AS in March 2023.

7.38. The Committee noted the prevalence of AS in New Zealand is not well described; however, internationally AS presents in approximately 0.1-0.32% of the population (Dean et al Rheumatology (Oxford). 2014;53;650-7)

7.39. The Committee noted that there is a strong association between the HLA-B27 allele and AS, with up to 90% of those with AS being positive for the allele. The Committee noted that the allele is less common in Māori with a frequency of approximately 6.5% compared to 9.2% in non-Māori (Roberts et al. Arthritis Res Ther. 2013;15:R158).The Committee noted in one New Zealand specialist clinic, approximately 10% of individuals treated were Māori, whilst the population of the area was approximately 23.5% Māori, and the Committee did not consider there to be evidence that Māori are overrepresented in the AS population (White et al. N Z Med J. 2019;132:38-47).

7.40. The Committee considered it is unclear whether health beliefs and healthcare access for Māori, Pacific peoples, people living in low decile or rural settings, or populations that are mobile, affect diagnosis rates for AS, and access to biologic treatments.

7.41. The Committee noted that AS leads to a significant loss in quality of life. The Committee noted White et al. 2019, a study of 81 individuals with AS. The Committee noted of these, 48% received biologic treatment and 86% were positive for the HLA-B27 allele. The study reported >80% experienced pain, whilst 50% reported difficulties with activities of daily living.

7.42. The Committee noted approximately 10-15% of those with AS did not receive relief from symptoms despite biologic treatments.

Health benefit

7.43. The Committee noted it had had previously reviewed evidence of the health benefit of secukinumab in February 2018, and had deferred making a recommendation pending publication of results of the SURPASS trial.

7.44. The Committee noted unpublished results provided for SURPASS, a randomised controlled phase 3b SURPASS study of secukinumab as first-line biologic treatment in AS, which included 859 individuals treated with either secukinumab 150 mg (*n*=287), 300 mg (*n*=286), or adalimumab biosimilar (*n*=286).

7.44.1. The Committee noted the Baraliakos et al. Poster ACR Convergence 2022 conference poster, which reported the following results at 104 weeks:

- At week 104, the proportion with no radiographic progression (CFB-mSASSS ≤0.5) was 66.1%, 66.9%, and 65.6% in the secukinumab 150 mg, 300 mg, and adalimumab arms, respectively.
- Mean change from baseline modified Stoke AS Spinal Score (mSASSS) was 0.54, 0.55, and 0.72 in the secukinumab 150 mg, 300 mg, and adalimumab arms, respectively.
- Overall, 56.9%, 53.8%, and 53.3% of participants with baseline ≥1 syndesmophyte(s) in the secukinumab 150 mg, 300 mg, and adalimumab arms, respectively, did not develop new syndesmophyte(s).
- At week 16, mean (SE) change from baseline-MRI Berlin sacroiliac joint scores were -1.22 (0.14), -1.10 (0.14), and -1.51 (0.14), and mean change from baseline MRI spine scores were -1.43 (0.14), -1.59 (0.15), -2.31 (0.15) in the secukinumab 150 mg, 300 mg, and adalimumab arms, respectively.
- Overall, 79.7%, 81.8%, and 84.2% had ≥1 adverse event (AE), and 14.0%, 10.2%, and 11.2% had serious AEs in the secukinumab 150 mg, 300 mg, and adalimumab biosimilar arms, respectively.

7.44.2. The Committee noted the Baraliakos X. et al POS1115 ARD 2023;82:882-3 conference poster, which reported the following results at 104 weeks for subgroups at baseline comprising high-sensitivity c-reactive protein (hsCRP) ≥5 mg/L (CRP+), hsCRP <5 mg/L (CRP−), presence of syndesmophyte(s) (Synd+), absence of syndesmophyte(s) (Synd−), and CRP+Synd+:

- 653 (76%) were CRP+, 627 (73%) were Synd+, and 466 (54%) were CRP+Synd+ at baseline.
- Demographic and baseline disease characteristics were largely balanced across subgroups and treatment arms (except for the Synd− group, in which mean age, proportion of males, and mean time since diagnosis were lower than in other subgroups).
- Spinal radiographic progression was low with no notable difference between treatment arms regardless of specific predictive factors for progression (syndesmophytes/elevated CRP). Subgroups without predictive factors (especially Synd−, followed by CRP−) had lower rates of radiographic progression.

7.45. The Committee noted that there had been a number of large-scale clinical trials that included different doses of secukinumab. The Committee considered these trials did not show a significant difference in the health benefit derived from secukinumab administered at a dose of 75 or 150 mg/month; however, there may potentially be a trend towards overall better clinical outcomes at a dose of 150 mg/month.

7.46. The Committee noted that in the SURPASS trial there was no significant difference between treatment arms in the primary endpoint of radiological progression.

7.47. The Committee considered that whilst radiological progression is a surrogate endpoint, there is reasonable evidence to correlate radiological progression to disease status, and it is a relevant endpoint for clinical trials investigating treatments for AS. The Committee noted Bath Ankylosing Spondylitis Disease Activity Index score is also a common clinical end point in trials for AS.

7.48. The Committee noted the SURPASS trial was not fully blinded, with clinicians blinded only to the dose rather than pharmaceutical administered.

7.49. The Committee noted evidence from the SURPASS trial did not suggest an increase in dose from 75 or 150 mg/month to 300 mg/month improved health outcomes.

7.50. The Committee considered the loading dose appeared to play a significant role in the early clinical response observed at 24 weeks.

7.51. The Committee considered the safety profile of secukinumab has been shown to be favourable over time, with no new signals since the Committee reviewed the application in 2018. The Committee noted the signals and safety profile were similar to funded tumour necrosis factor (TNF) alpha inhibitors.

7.52. The Committee noted the following studies:

- Morzo-Ortega et al. Lancet Rheumatol 2020;2: e339–46
- Braun et al. Rheumatology (Oxford). 2019;58:859-68.
- Baraliakos et al. RMD Open. 2019;5:e001005
- Deodhar et al. Clin Exp Rheumatol. 2019;37:260-9
- Pavelka et al. Arthritis Res Ther. 2017;19:285
- Kishimoto et al. Mod Rheumatol. 2020;30:132-40
- Tseng et al. Front Immunol. 2020 Nov:11:56174
- Huang et al. Chin Med J (Engl). 2020;133:2521-31.
- Lebwohl et al. Br J Dermatol. 2021;185:935-44
- Deodhar et al. Arthritis Res Ther. 2019;21:111
- Schreiber et al. Ann Rheum Dis. 2019;78:473-79.
- Azadeh et al. Inflammopharmacology. 2022;30:435-51
- Deodhar et al. J Rheumatol. 2020;47:539-47
- Lee et al. Pharmacology. 2022;10:537-44
- Yu et al. BioDrugs. 2020;34:669-79
- Zhou et al. Mediators Inflamm. 2020:1639016
- Katsevman et al. Monoclon Antib Immunodiagn Immunother. 2020;39:160-6
- Wang et al. Clin Rheumatol. 2021;40:3053-65
- Yin et al. Arthritis Res Ther. 2020;22:111

7.53. The Committee noted that Kvien et al. Arthritis Care Res (Hoboken). 2022;74:759-67 reported a significant ($p<0.05$) improvement in fatigue scores at 16 weeks in those treated with secukinumab, which was maintained at 156 weeks. The Committee noted the trial comprised of a single arm and did not compare against current treatments.

7.54. The Committee considered those with AS and concomitant psoriatic arthritis may benefit more from secukinumab, due to its reported benefits in treating the dermatological presentations of psoriasis, however the extent of benefit was uncertain, and further advice on this individual subgroup would be needed.

7.55. The Committee considered results of the SURPASS, as well as other evidence, and considered there was no evidence supporting a benefit of secukinumab compared to TNF-inhibitors in a first line setting.

7.56. The Committee considered the Rheumatology Special Advisory Committee may wish to review applications for this and other treatments for non-radiological AS, as current clinical trials also include this population.

7.57. The Committee noted that the updated clinical trial evidence was not published in peer reviewed scientific publications. The Committee noted its desire to review published data, that has been peer reviewed, submitted in support of applications. The Committee reiterated the challenges of publication bias and the need to prevent it.

Suitability

7.58. The Committee noted that once maintenance dosing is reached, secukinumab required less frequent administration compared with currently funded anti-TNF-alpha treatments, being administered every 4 weeks compared with every 1-2 weeks respectively.

7.59. The Committee considered the subcutaneous formulation may relieve any pill burden potentially experienced by individuals currently receiving funded, orally administered treatments. The Committee considered this may support treatment adherence.

Cost and savings

7.60. The Committee noted that secukinumab is more expensive than current first-line biologics for AS and considered that cost-neutrality would be unlikely given the availability of the biosimilar adalimumab.

Funding criteria

7.61. The Committee considered that the Special Authority continuation criteria for AS treatments, should be amended to a “reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain VAS by 2 cm or more”, to align with international guidelines.

7.62. The Committee noted that most individuals have at least three months of physiotherapy and trial non-steroidal anti-inflammatories for three months before biologic treatment. The Committee therefore considered the Special Authority criteria of disease being present for six months or more to be appropriate. The Committee considered this should be reviewed by the Rheumatology Specialist Advisory Committee.

Summary for assessment

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

Population	People with AS requiring first-line biologic treatment
Intervention	Secukinumab at a dose of 150 mg at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter
Comparator(s)	*First-line anti-TNFs, either*: - Adalimumab, 40 mg every fortnight, or - Etanercept, 50 mg every week
Outcome(s)	Similar rates of clinical response and radiographic progression as currently funded first-line anti-TNFs
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

8. Budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler for maintenance treatment to prevent exacerbations, relieve symptoms in adults with moderate to very severe COPD

Application

8.1. The Advisory Committee reviewed the application for budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler for maintenance treatment to prevent exacerbations, relieve symptoms in adults with moderate to very severe COPD.

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

Recommendation

8.3. The Advisory Committee **recommended** that budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler for maintenance treatment to prevent exacerbations, relieve symptoms in adults with moderate to very severe COPD be listed as cost neutral to the pricing of current funded triple therapy agents (any combination of inhaled corticosteroid (ICS), long-acting beta-agonist (LABA) and long-acting muscarinic-antagonist (LAMA)) available, subject to the following Special Authority criteria:

> **Initial application** — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 1. Patient has a diagnosis of COPD confirmed by spirometry; and
> 2. Patient is currently receiving an ICS/LABA or LAMA/LABA or multiple inhaler triple therapy treatment; and
> 3. Any of the following:
>   3.1. Patient has a COPD Assessment Test (CAT) score greater than 10; or
>   3.2. Patient has had greater than 2 exacerbations in the previous 12 months; or
>   3.3. Patient has had an eosinophil count greater than or equal to 0.3 x 10^9 cells/L in the previous 12 months
>
> **Renewal** — from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:
> Both:
> 1. Patient is adherent with medication; and
> 2. The treatment remains appropriate and the patient is benefitting from treatment.

8.4. The Advisory Committee considered the following in making their recommendation:

- Single inhaler triple therapy (SITT) improves adherence compared to multiple inhaler triple therapy (MITT) but does not improve clinical outcomes.
- COPD inequitably impacts Māori, Pacific peoples, and those living in areas of high deprivation most.
- Budesonide, formoterol and glycopyrronium inhalers are currently funded for the treatment of COPD.

- If funded, this inhaler would displace the use of three drug components (any combination of funded ICS, LABA and LAMA inhaler(s)) administered via multiple inhalers but would not alter the treatment paradigm.
- ICS therapy should not be used for extended periods in people with COPD due to the increased risk of infection.
- Review of the Special Authority criteria by the Respiratory Specialist Advisory Committee to advise an appropriate way to include the risk of infection in the renewal criteria.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler (BGF MDI) for maintenance treatment to prevent exacerbations and relieve symptoms in adults with moderate to very severe COPD on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

8.6. The Committee considered that Māori are inequitably burdened by COPD with a higher age-standardised prevalence, younger age at diagnosis and higher rates of hospitalisation with COPD compared to non-Māori, non-Pacific and non-Asian peoples (non-MPA) (Impact of Respiratory disease in New Zealand: 2020 update. Asthma and Respiratory Foundation New Zealand. August 2021).

8.7. The Committee noted a supplier estimate that nearly half the people that would use this inhaler would be Māori.

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

8.8. The Committee discussed the impact of funding of BGF MDI for maintenance treatment to prevent COPD exacerbations, relieve symptoms in adults with moderate to very severe COPD on Pacific, disabled, and underserved populations. The Committee considered that Pacific peoples are inequitably burdened by COPD with a higher age-standardised prevalence, younger age at diagnosis and higher rates of hospitalisation with COPD compared to non-Māori, non-Pacific and non-Asian peoples (non-MPA) (Asthma and Respiratory Foundation New Zealand. 2021).

8.9. The Committee noted that those living in areas of high deprivation are also more likely to be hospitalised with COPD (Asthma and Respiratory Foundation New Zealand. 2021).

Background

8.10. The Committee noted its previous review of a SITT for COPD in May 2019 (fluticasone/vilanterol/umeclidinium inhaler (Trelegy)). The Committee noted that the (then) Respiratory Subcommittee also reviewed this application in October 2020.

8.11. The Committee noted that the Respiratory Subcommittee recommended Trelegy be funded at cost-neutral to the pricing of the same components received from multiple inhalers subject to Special Authority criteria.

8.12. The Committee noted Members' previous considerations from May 2019 that in the context of caring for people with COPD, there were issues that may be more important than the funding of additional inhalers, including addressing the accessibility of pulmonary rehabilitation programmes, influenza vaccination, education, and access to services and smoking cessation support for people with COPD.

Health need

8.13. The Committee noted that COPD is a heterogenous lung condition characterised by chronic respiratory symptoms due to abnormalities of the airways and/or alveoli that

cause persistent, often progressive, airflow obstruction. The Committee noted that severity of COPD is measured using a number of measures including forced expiratory volume in one second (FEV1) (Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2023 Report).

8.14. The Committee noted that people with moderate to very severe COPD were defined as those whose condition has not responded to long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) dual therapy, resulting in two or more exacerbations in the previous 12 months. The Committee noted New Zealand guidelines which suggest that these people are escalated to triple inhaler therapy which includes an inhaled corticosteroid (ICS), LABA and LAMA (Hancox et al. New Zealand COPD Guidelines: Quick Reference Guide. 2021). The Committee noted that GOLD stage 3 and 4 COPD are associated, on average with the loss of 2.2 years and 5.8 years of life respectively and additional decrements in health-related quality of life (Shavelle et al. Int J Chron Obstruct Pulmon Dis. 2009;4:137-48).

8.15. The Committee considered that Māori and Pacific peoples are inequitably burdened by COPD with a higher age-standardised prevalence, younger age at diagnosis and higher rates of hospitalisation with COPD compared to non-Māori, non-Pacific and non-Asian peoples (non-MPA). The Committee considered that those living in areas of high deprivation are also more likely to be hospitalised with COPD (Asthma and Respiratory Foundation New Zealand. 2021).

8.16. The Committee noted that COPD, as a respiratory disease, is considered to be part of Hauora Arotahi; Pharmac's Māori Health areas of focus.

8.17. The Committee noted a supplier estimate that nearly half the people that would use this inhaler would be Māori.

Health benefit

8.18. The Committee noted that all therapeutic components are available in funded inhalers including dual therapy inhalers or single therapy inhalers. The Committee considered that these inhalers can be used in combination (two or three inhalers) for triple therapy for COPD known as multiple inhaler triple therapy (MITT). The Committee considered that a lack of funded SITT does not preclude the appropriate use of triple therapy.

8.19. The Committee noted a retrospective cohort study analysing electronic health records from Spain to identify people who use MITT or SITT and their relative persistence, exacerbations and health care resource use in people with COPD (Alcázar-Navarrete et al. Chest. 2022;162:1017-29). The Committee noted that there were reported benefits in all-cause mortality (hazard ratio: 0.67; 95% CI = 0.63-0.71, *P*=0.027) and reduced health resource use (mean annual cost savings: €403 vs MITT), but noted that these results conflicted with published meta-analyses.

8.20. The Committee noted a multicentre, prospective cohort study in hospitals in China assessing treatment persistence, adherence and exacerbation rates over 12 months in people using SITT and MITT (Lin et al. Front Pharmacol. 2023;14:1147985). The Committee noted that the SITT group had lower reported moderate to severe exacerbations compared to the MITT group (hazard ratio: 0.729 (95% CI, 0.593-0.898 (*P*=0.003)). The Committee noted that in this study persistence (regardless of SITT or MITT) was associated with fewer future exacerbations (hazard ratio: 0.401 (95% CI, 0.325-0.495 (*P*=0.001)) and reduced mortality (hazard ratio: 0.405 (95% CI, 0.205-0.800 (*P*=0.009)) compared to non-persistence. The Committee considered that this study was at risk of bias due to the choice of SITT or MITT being decided by the treating clinician based on unknown preferences, making the reported outcomes difficult to interpret.

8.21. The Committee noted a systematic literature review and indirect comparison network meta-analysis of the efficacy of BGF MDI versus other ICS/LAMA/LABA triple combinations in COPD (Ferguson et al. Adv Ther. 2020;37:2956-75). The Committee noted that incidence rates of moderate to severe exacerbations in the group using BGF

MDI compared to other triple therapy combinations as SITT or MITT was reported to not show a statistically significant difference.

8.22. The Committee noted an indirect comparison network meta-analysis of the fluticasone furoate/umeclidinium/vilanterol triple therapy compared with other therapies for the treatment of COPD (Ismaila et al. Adv Ther. 2022;39:3957-78). The Committee noted that this study reported SITT was superior to MITT in reducing moderate to severe exacerbation rates and that fluticasone furoate/umeclidinium/vilanterol SITT was superior to BGF MDI. The Committee noted that the trials included in this study were the same as those included in Ferguson et al. (above). The Committee noted that this was a supplier sponsored study.

8.23. The Committee noted an indirect comparison network meta-analysis and IBiS score comparing the efficacy and safety profile of triple fixed-dose inhaler combinations in COPD using data from dual versus triple therapy randomised control trials (Rogliani et al. J Clin Med. 2022;11(15)). The Committee noted that the comparison of fluticasone furoate/umeclidinium/vilanterol and BGF MDI found no statistically significant difference in clinical outcomes (exacerbation rate or FEV1). The Committee considered that SITTs of varying composition of ICS, LABA, and LAMA, are of comparable efficacy in the context of COPD.

8.24. The Committee noted a multicentre, randomised open-label, phase IV trial comparing SITT and MITT in moderate to very severe COPD (Zhang et al. Clin Ther. 2022;44:859-73). The Committee noted that a statistically significant difference in FEV1 was reported between those that used SITT and MITT (mean difference: 0.02 L; 95% CI, 0.00-0.05L; *P*<0.01) however, this was below the recognised Minimum Clinically Important Difference (MCID).

8.25. The Committee noted a meta-analysis assessing the rate of moderate to very severe COPD exacerbations comparing SITT and MITT (Lai et al. Int J Chron Obstruct Pulmon Dis. 2019;14:1539-48). The Committee noted that there were no significant differences reported between SITT and MITT with respect to COPD exacerbation, changes in lung function and quality of life.

8.26. The Committee noted a multicentre, randomised, open-label, phase IV effectiveness study comparing fluticasone/umeclidinium/vilanterol 100/62.5/25 µg via the ELLIPTA inhaler with a clinician's choice of any approved non-ELLIPTA MITT in usual COPD clinical practice in five European countries (Halpin et al. ERJ Open Res. 2021;7(2)). The Committee noted that a statistically significant difference in FEV1 was reported between those that used SITT and MITT (mean treatment difference 50 mL, 95% CI 26–73 mL; *P*<0.001), but this was below the recognised MCID. The Committee considered that this trial did not include the drug proposed for funding but did illustrate the effect of SITT overall.

8.27. The Committee considered that the benefit of SITT is the increase in persistence and adherence of people using inhaled therapy. The Committee considered that the evidence was of moderate strength and quality to demonstrate non-inferiority to various MITT and SITT options. The Committee considered that there was no good quality evidence that associates increased adherence and improved clinical outcomes (eg reduction in exacerbations or difference in FEV1).

8.28. The Committee considered that there was no difference in clinical efficacy of MDI compared to dry powder inhaler (DPI) despite lower drug distribution at the pulmonary alveolar level with DPIs.

Suitability

8.29. The Committee considered that SITT gives greater ease of use over MITT due to the single inhaler required. The Committee considered that adherence would be improved as a result of ease of use.

8.30. The Committee noted that the micronised MDI required regular washing by the person using it to allow the continued delivery of therapy.

8.31. The Committee noted that these inhalers can be used with a spacer that requires less co-ordination of inhalation and depressing of the canister and allows people to breathe normally while using their inhalers.

8.32. The Committee noted that Breztri Aerosphere is a micronised MDI that contains a fluorocarbon as the propellant. The Committee noted that fluorocarbons are potent greenhouse gases that have long atmospheric lifetimes (United States Environmental Protection Agency. Updated June 2023). The Committee considered that if the comparator combination was two MDIs then this proposal would decrease the propellants' used overall. The Committee noted that the fluticasone furoate/umeclidinium/vilanterol SITT considered in May 2019 is a DPI that does not contain any fluorocarbons.

Cost and savings

8.33. The Committee considered that BGF MDI would replace current MITT options containing budesonide, glycopyrronium and formoterol. The Committee noted that these combinations (and formulations) varied as there was a range of funded options for each agent. The Committee noted that this range of choice can create complexity for prescribers.

Funding criteria

8.34. The Committee considered that the Special Authority criteria should be the same as recommended by the Respiratory Subcommittee recommended in October 2020. The Committee considered that the Special Authority criteria of all single inhaler triple therapy inhaler criteria considered for funding should be aligned.

8.35. The Committee considered that the funding criteria as recommended by the Respiratory Subcommittee are wider than the eligibility criteria and study populations in the randomised control trials, but considered that this is appropriate and based on the health need of people with COPD requiring triple inhaler therapy.

8.36. The Committee considered that ICS therapy should not be used for extended periods in people with COPD due to the increased risk of infection. The Committee considered that this should be included in the renewal criteria to be advised by the Respiratory Specialist Advisory Committee.

Summary for assessment

8.37. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for budesonide, glycopyrronium and formoterol (eformoterol) metered dose inhaler if it were to be funded in New Zealand for maintenance treatment to prevent exacerbations, relieve symptoms in adults with moderate to very severe COPD. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with moderate to very severe COPD requiring triple therapy with inhaled corticosteroids (ICS), long-acting beta-adrenoceptor agonists (LABA) and long-acting muscarinic antagonists (LAMA).
Intervention	Breztri Aerosphere (160mcg budesonide, 7.2mcg glycopyrronium and 5mcg eformoterol aerosol metered dose inhaler) • Two inhaled actuations, twice daily Duration of treatment is indefinite so long as treatment remains appropriate, and the individual is benefitting from treatment.
Comparator(s) (NZ context)	Comparator regimens may include: • Vannair 200/6, with Seebri Breezhaler • Symbicort Turbuhaler 200/6, with Seebri Breezhaler • Duoresp Spiromax 160/4.5, with Seebri Breezhaler • Pulmicort 200, with Oxis Turbuhaler, and Seebri Breezhaler
Outcome(s)	Single inhaler triple therapy improves persistence compared to multiple inhaler triple therapy but does not improve clinical outcomes. No significant difference in health benefits or risks associated with receiving budesonide, formoterol and glycopyrronium in a single inhaler compared to receiving the same components from multiple inhalers.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

9. Guselkumab for first-line biologic treatment of psoriatic arthritis

Application

9.1. The Advisory Committee reviewed the application for guselkumab for the treatment of psoriatic arthritis.

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** that guselkumab be **declined** for funding in the **first-line biologic** treatment of psoriatic arthritis.

9.4. The Advisory Committee **recommended** that guselkumab be funded if **cost neutral** to secukinumab in the **second-line biologic** treatment of psoriatic arthritis subject to the following Special Authority criteria:

> **Initial application — (psoriatic arthritis – second-line biologic)** only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. The patient has had an initial Special Authority approval for adalimumab, infliximab and/or etanercept for psoriatic arthritis; and
> 2. Either
> 2.1. The patient has experienced intolerable side effects from a reasonable trial of adalimumab and/or etanercept and/or infliximab and/or secukinumab; or
> 2.2. The patient has received insufficient benefit from adalimumab, infliximab, etanercept, or secukinumab to meet the renewal criteria for them as first-line biologic agents for psoriatic arthritis.

Renewal — (psoriatic arthritis – second-line biologic) only from a rheumatologist or practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:
   1.1. Following 3 to 4 months' initial treatment, the patient experiences at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
   1.2. The patient experiences at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to prior guselkumab treatment in the opinion of the treating physician; and
2. Guselkumab to be administered at doses no greater than 100 mg every 8 weeks.

9.5. The Advisory Committee considered the following when making its recommendation:

- The health need of individuals with psoriatic arthritis and their need for additional treatment options
- The health benefit in treatment of psoriatic arthritis
- The increased suitability of the guselkumab compared to currently funded options.

Discussion

Māori impact

9.6. The Committee discussed the impact of funding guselkumab for the treatment of psoriatic arthritis (PsA) on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes. The Committee noted PsA is not a Hauora Arotahi. The Committee considered there was no evidence that PsA disproportionally affects Māori. However, the Committee considered it is unclear how health beliefs and healthcare access impacts on the diagnosis rates for PsA, and access to biologic treatments.

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

9.7. The Committee discussed the impact of funding guselkumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee considered it is unclear how health beliefs and healthcare access for Pacific peoples, low decile, mobile and rural populations impact on diagnosis rates for PsA, and access to biologic treatments.

Background

9.8. The Committee noted guselkumab was considered in June 2023 by the Dermatology Advisory Committee and recommended as a high priority for funding for first- and second-line treatment of moderate to severe plaque psoriasis.

Health need

9.9. The Committee noted it had reviewed the health need of individuals with PsA in May 2022 and by the Rheumatology Advisory Committee in March 2023.

9.10. The Committee noted approximately 860 people in New Zealand receive biologic disease-modifying antirheumatic drugs (bDMARD) for PsA.

9.11. The Committee noted many individuals switch treatment between different biologics, with secukinumab used in first line by approximately 20% of people.

9.12. The Committee noted Ogdie et al, RMD Open 2020;6:e001321, a study in 19 people with PsA that reported the most bothersome aspects of PsA were the effects on daily activities, sleep disturbance, physical disability, and feelings of frustration.

Health benefit

9.13. The Committee noted DISCOVER-1, a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial in 381 individuals with PsA. The trial compared guselkumab 100 mg every 4 weeks; guselkumab 100 mg at weeks 0, 4, then every 8 weeks; or matching placebo. The Committee noted the following publications reporting study results.

9.13.1. The Committee noted Deodhar et al. Lancet. 2020;395:1115-25, which reported the following results at 24 weeks:

- American College of Rheumatology 20% improvement (ACR20) at week 24: guselkumab every 4 weeks group (76 [59%] of 128 [95% CI 50-68]) ,every 8 weeks group (66 [52%] of 127 [43-61]) vs placebo group (28 [22%] of 126 [15-30]), with percentage differences versus placebo of 37% (95% CI 26-48) for the every 4 weeks group and 30% (19-41) for the every 8 weeks group (both *P*<0.0001).

- No serious adverse effects occurred in those receiving guselkumab every 4 weeks, 3% of those receiving guselkumab every 8 weeks experienced serious adverse effects, and 4% of those receiving placebo. One person in the placebo group died from cardiac failure and two had serious infections.

9.13.2. The Committee noted Ritchlin et al. RMD Open. 2021;7:e001457, which reported the following results at 52 weeks:

- There were 90% of participants who completed the study. Numerical increases in the proportions achieving ACR20 were observed post-week 24, reaching 73% and 60% for Q4W and Q8W, respectively, by week 52.

- Proportions achieving ACR50/ACR70/skin responses and minimal disease activity were maintained, as were improvements in physical function and health-related quality of life, through week 52 in the guselkumab-randomised arm.

- Response to guselkumab was maintained in both tumour necrosis factor inhibitor (TNFi)-naïve and TNFi-experienced.

9.14. The Committee noted the DISCOVER-2 double-blind, randomised, placebo-controlled phase 3 trial in 741 people. The Committee noted the Mease et al. Lancet. 2020;395:1126-36, McInnes et al. Arthritis Rheumatol.2021;73:604-16, and McInnes et al. Arthritis Rheumatol. 2022;74:475-85 publications, which reported results at 24 weeks, 1 year and 100 weeks respectively:

- Significantly greater proportions in the guselkumab every 4 weeks group (156 [64%] of 245 [95% CI 57-70]) and every 8 weeks group (159 [64%] of 248 [58-70]) than in the placebo group (81 [33%] of 246 [27-39]) experienced an ACR20 response at week 24 (percentage differences vs placebo 31% [95% CI 22-39] for the every 4 weeks group and 31% [23-40] for the every 8 weeks group; both *P* <0.0001).

- Most participants (88%) completed week 100. Across groups of guselkumab-treated individuals (including placebo-guselkumab crossover group), 68-76% experienced treatment response measured by ACR20, 48-56% by ACR50, 30-36% by ACR70, 55-67% by an IGA score of 0, 62-70% experienced enthesitis resolution, and 72-83% dactylitis resolution. Mean changes in the Sharp/van der Heijde modified score for PsA from weeks 52 to week 100 (range 0.13-0.75) indicated low rates of radiographic progression extended through week 100.

9.15. The Committee noted the COSMOS phase 3b, randomised, controlled study in 285 people over 56 weeks (Coates et al. Ann Rheum Dis.2022;81:359-69). The study reported at week 24 a statistically significantly higher proportion of individuals receiving guselkumab than placebo (experienced ACR20 (44.4% vs. 19.8%, difference (95% CI): 24.6% (14.1% to 35.2%); multiplicity-adjusted *P* <0.001). Guselkumab was superior to placebo for each key secondary endpoint (multiplicity-adjusted *P* <0.01).

9.16. The Committee noted the endpoints across all trials were clinically relevant; however, the variation between endpoints made direct comparisons difficult. The Committee noted x-rays were not reviewed in DISCOVER-2 but were in DISCOVER-1.

9.17. The Committee noted trial participant baseline disease severity varied between DISCOVER-1 and DISCOVER-2, with individuals with clinically less severe disease included in DISCOVER-1, and individuals with more complex disease included in DISCOVER-2.

9.18. The Committee noted there were a small number of individuals in the COSMOS trial.

9.19. The Committee noted the trial data suggests there was a health benefit in those whose disease had not responded to TNF inhibitors.

9.20. The Committee noted the sustained and improved response, regardless of baseline demographics and previous treatments.

9.21. The Committee noted the following studies:

- Curtis et al. Adv Ther. 2022;39:4613-31.
- Curtis et al. Adv Ther. 2022;39:4632-44.
- Gottlieb et al. RMD Open. 2023;9:e002789
- Schett et al. Rheumatol Ther. 2022;9:1017-30
- Orbai et al. Patient. 2022;15:657-68
- McGonagle et al. Rheumatology (Oxford). 2021;60:5337-50.
- Rahman et al. J Rheumatol. 2021;48:1815-23.
- Sweet et al. RMD Open. 2021;7:e001679
- Rahman et al. Arthritis Res Ther. 2021;23:190
- Ritchin et al. RMD Open. 2022;8:e002195
- Coates et al. Rheumatology (Oxford). 2023;62:606-16.
- McGonagle ACR Open Rheumatol. 2023;5:227-40.
- Mease et al. Rheumatology (Oxford). 2021;60:2109-21
- McInnes et al. RMD Open. 2022;8:e002074.
- Song et al. Int J Clin Pharmacol Ther. 2021;59:433-41

9.22. The Committee noted that there was a lack of ethnic diversity within the trial populations, with participants only recruited from the Northern Hemisphere. The Committee noted that there was a small number in the trial who developed melanomas, which is a particular health risk and concern in the Australasian setting. The Committee noted this was a small number and considered it should be monitored in longer term follow up data.

9.23. The Committee noted Mease et al. Rheumatology (Oxford). 2023;62:1417-25, an indirect comparison that reported guselkumab offered a better skin efficacy than many other targeted therapies for PsA, as well as arthritis efficacy that is comparable to IL-17A, JAK,

and subcutaneous TNF inhibitors. The Committee noted that the analysis compared different disease severity populations, which may confound results, in addition to noting the limitations of indirect comparisons in general.

9.24. The Committee noted guselkumab appeared to have a favourable safety profile similar to most other agents for treating PsA.

9.25. The Committee noted there were no trials directly comparing guselkumab with other funded treatments for PsA.

9.26. The Committee considered guselkumab appears to be non-inferior to other funded treatments including secukinumab, etanercept, infliximab, and adalimumab, in terms of safety and efficacy. However, the Committee considered the data remains immature and that further long-term information is necessary to confirm the apparent trend.

9.27. The Committee considered there may be a class effect for P19 subunit IL-23 inhibitors in the treatment of PsA; however, the data is immature, and longer term follow up data is needed.

9.28. The Committee considered that people who would receive the most health benefit from guselkumab would be those with significant psoriatic skin involvement, those for whom TNF inhibitors would be contraindicated, or who experienced intolerable side effects or insufficient clinical benefit from TNF inhibitors.

9.29. The Committee considered guselkumab to have similar efficacy as secukinumab, especially in individuals with PsA with significant skin involvement, which has a similar mechanism of action.

Suitability

9.30. The Committee considered a switch to guselkumab may result in a reduction in the number of injections an individual would have to administer or receive, and their treatment burden, compared to other funded biologics for PsA.

Cost and savings

9.31. The Committee considered the discontinuation rates reported in DISCOVERY 1 and 2 probably reflect the expected discontinuation rates for people receiving biologics for PsA in New Zealand.

9.32. The Committee noted that guselkumab would generally be used in combination with other treatments including methotrexate, however, it could be used as a monotherapy if other treatments were not tolerated.

Summary for assessment

9.33. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for guselkumab if it were to be funded for second line biologic treatment in New Zealand for PsA. 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 whose condition has not responded adequately to, or for whom conventional DMARDs and one or more tumour necrosis factor (TNF) inhibitors were not tolerated (biologic-experienced population)
Intervention	Guselkumab alone or in combination with methotrexate (MTX) 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. In case of treatment non-response, people may proceed to a subsequent biologic.
Comparator(s)	Potential comparators: • Secukinumab: 300 mg weekly for five weeks and monthly thereafter • Adalimumab: 40 mg every two weeks • Etanercept: 50 mg once per week • Infliximab: 5 mg/kg given at weeks 0, 2 and 6, followed by a maintenance dose every 8 weeks If all biologic treatments fail, people receive Best Supportive Care
Outcome(s)	Arthritis efficacy and skin efficacy comparable to funded biologics (secukinumab, adalimumab, etanercept, infliximab), as measured in ACR 20/50 response and PASI 75/90/100 response, with comparable rates of severe or serious adverse events (Mease et al. Rheumatology 2023)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

10. Cladribine for relapsing remitting multiple sclerosis (RRMS)

Application

10.1. The Advisory Committee reviewed the resubmission from Merck for cladribine (Mavenclad) for the treatment of relapsing-remitting multiple sclerosis (RRMS). The Advisory Committee also considered a supporting submission from Multiple Sclerosis New Zealand (MSNZ) which reported the consumer perspective on cladribine for RRMS.

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

Recommendation

10.1. The Advisory Committee **recommended** that cladribine be listed only if **cost neutral** to a weighted average of the currently funded RRMS treatments it is likely to displace.

10.2. The Advisory Committee considered the following when making its recommendation:

- The strengths and limitations of the available evidence for the effectiveness of cladribine, being mostly longitudinal observational registry data limited by the MS population recorded in the registry, which varies in timing of receiving treatment and the availability of treatments between regions, with a lack of direct head-to-head evidence available to compare cladribine with funded MS treatments.

- The suitability of the oral formulation and dosing regimen, considering that oral four to five day 'bursts' of treatment for each year of treatment provides material suitability benefits over currently funded MS treatments.

Discussion

Māori impact

10.3. The Committee discussed the impact of funding cladribine for the treatment of RRMS on Māori health outcomes. The Committee noted that MS is not one of Pharmac's 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

10.4. The Committee discussed the impact of funding cladribine 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). The Committee noted that MS causes substantial physical disability with need for health services, and people with MS are part of the disabled people and tāngata whaikaha Māori populations.

Background

10.5. The Committee noted a supplier application from Merck for cladribine was first considered by the Neurological Advisory Committee (then Subcommittee) in July 2018. The Committee noted that the Neurological Advisory Committee recommended that the application for cladribine be declined, primarily due to uncertainty regarding retreatment with cladribine following the initial treatment course.

10.6. The Committee noted in November 2019 PTAC reviewed a resubmission from the applicant and recommended that cladribine be funded only if cost neutral to fingolimod, taking into account that 20% of patients may require redosing with cladribine at 2 years, with the remaining 80% likely requiring redosing at 4 years. The Committee noted this recommendation was based on the evidence relating to cladribine efficacy at the time, fingolimod being the most likely comparator, and expert opinion regarding retreatment rates.

Health need

10.7. The Committee noted that as per the submission from MSNZ, over 4100 people are currently diagnosed with MS in New Zealand, with an average age at diagnosis of 38 years. The Committee noted advice provided in 2018 for ocrelizumab for RRMS on the health need of people with RRMS and their families and whānau, and considered there was no new advice to be provided about health needs at this time.

Health benefit

10.8. The Committee noted that cladribine is a nucleoside analogue of deoxyadenosine that is resistant to deamination by adenosine deaminase. The Committee noted that the mechanism of action in the setting of RRMS is not fully elucidated however its selective effect on lymphocytes is thought to interrupt the cascade of immune events central to MS.

10.9. The Committee noted cladribine (Mavenclad) is approved by Medsafe for the treatment of RRMS to reduce the frequency of clinical relapses and to delay the progression of physical disability. The Committee noted the recommended cumulative dose is 3.5 mg/kg over two years, administered as one treatment course of 1.75 mg/kg per year. The Committee noted each treatment course consists of two treatment weeks, one at the beginning of the first month (week one) and one at the beginning of the second month (week five) of the respective treatment year, and each treatment week consists of four or five days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. The Committee considered that the oral

administration and infrequent dosing schedule (which provides long 'treatment free' periods) were advantages of cladribine compared to currently funded treatment options for RRMS.

10.10. The Committee noted that in November 2019 it had reviewed the 96-week, double-blind, placebo-controlled, phase 3 CLARITY trial (Giovannoni et al. N Engl J Med. 2010;362:416-26) and the 2-year CLARITY Extension trial (Giovannoni et al. Mult Scler. 2018;24:1594-1604), which investigated the efficacy and safety of cladribine in patients with RRMS. The Committee noted it had considered the evidence showed efficacy of cladribine for RRMS, but considered there was unclear duration of health benefit, and unclear staging of treatment.

10.11. The Committee reviewed the long-term follow-up of the CLARITY Extension cohort (median 10.9 years) which reported on long-term mobility and disability beyond treatment courses received in CLARITY/CLARITY Extension (*N*=435) (Giovannoni et al. Mult Scler. 2023;29:719-30). The Committee noted that at 4-years since the last parent study dose, 63% of participants did not use another disease-modifying therapy, 48% showed no evidence of disease reactivation, and 33% both did not use another therapy and showed no evidence of disease reactivation.

10.12. The Committee noted results from a retrospective cohort study utilising data from the international MSBase registry, comparing cladribine tablets with other oral disease-modifying treatments for multiple sclerosis (fingolimod, dimethyl fumarate, or teriflunomide tablets) (Spelman et al. Mult Scler. 2023;29:221-35). The Committee noted the cohort of people initiating cladribine tablets had lower annualised relapse rates (ARRs) compared with the propensity-matched fingolimod cohort (ARR 0.09, 95% CI 0.07, 0.13 cladribine cohort matched to fingolimod versus ARR 0.15, 95% CI 0.12, 0.18 fingolimod matched to cladribine; *P*=0.016), the matched dimethyl fumarate cohort (ARR 0.10, 95% CI 0.07, 0.13 cladribine cohort matched to dimethyl fumarate versus ARR 0.15, 95% CI 0.11, 0.19 dimethyl fumarate matched to cladribine; *P*=0.031), and the matched teriflunomide cohort (ARR 0.09, 95% CI 0.06, 0.12 cladribine cohort matched to teriflunomide versus ARR 0.17, 95% CI 0.14., 0.21 teriflunomide matched to cladribine; *P*<0.001).

10.13. The Committee noted longitudinal observational data from the CLARINET-MS study which assessed the long-term effectiveness of cladribine tablets by following people with MS in Italy, using data from the Italian MS Registry (*n*=80) (Patti et al. Ther Adv Deurol. Disord. 2020;13). The Committee noted the probability of people being relapse free 12-months following cladribine treatment was 84.8%, 66.2% at 36 months following treatment, and 57.2% at 60 months following treatment.

10.14. The Committee noted results from a multicentre retrospective study conducted in the United Kingdom and Germany which assessed non-inferiority in relapse rates of cladribine tablets (*n*=610) versus fingolimod (*n*=485) in people with highly active relapsing MS (HA-RMS) over a 12-month period (Brownlee et al. Mult Scler Relat Disord. 2023;76:104791). The Committee noted the primary endpoint, ARR, was 0.10 for cladribine tablets and 0.14 for fingolimod with the cladribine:fingolimod adjusted ARR rate ratio (ie relative risk) being 0.68 (95% CI 0.42, 1.11). The Committee noted the authors' conclusion that given the entire ARR rate ratio 95% CI was less than the non-inferiority margin of 1.2, cladribine tablets were non-inferior to fingolimod.

10.15. The Committee also noted results from the following citations provided by the supplier:

- Albanese et al. Mult Scler Relat DIsord. 2022;68:104156
- Wu et al. EbioMedicine. 2022;81:104102
- Rog et al. J Neurol Neurosurg Psychiatry. 2022;93:e2
- Giovannoni at al. Drug Saf. 2020;43:635-43

10.16. The Committee considered the quality of the evidence of incremental effectiveness for cladribine for MS to be low. The Committee considered that as most available data is observational from disease registry data, the way that cladribine is dosed in short treatment courses can complicate assessment, particularly when examining incremental benefits beyond the effects of fingolimod and dimethyl fumarate. The Committee considered that the current evidence indicated that cladribine was likely to have similar overall efficacy in reducing ARR and delaying confirmed disability worsening (CDW) as currently funded treatments.

10.17. The Committee considered there is limited evidence to suggest that those who have become pregnant after a treatment course of cladribine have not experienced negative consequences to the foetus (Dost-Kovalsky et al. Mult Scler. 2023;29:461-5). However, the Committee noted that the authors concluded effective contraception for six months after the last cladribine dosing is necessary. The Committee noted the NZ cladribine datasheet's statement that no imbalance of adverse pregnancy outcomes between cladribine and placebo has been observed, but noted that cladribine nonetheless is contraindicated in pregnancy.

Suitability

10.18. The Committee considered that as an oral treatment, cladribine has the potential to relieve pressure on infusion services if used for people who would otherwise receive treatments administered via intravenous infusion. The Committee considered that the oral regimen may also provide benefit over possible subcutaneous treatment due to people's preference for oral administration over injections.

10.19. The Committee considered there was a suitability benefit from short treatment periods, providing extended treatment benefit without regular treatments. The Committee considered consequent benefits of short-term treatment periods include possibly reduced monitoring and follow up requirements, reduced clinic appointments required with neurology services, and reduced required travel time for those receiving treatment.

Cost and savings

10.20. The Committee considered the oral and infrequent administration regimen of cladribine (≤20 tablets per year) has the potential to benefit the health system, as people switching from IV natalizumab would no longer require infusions, which would reduce the burden on infusion-related service.

10.21. The Committee reiterated previous considerations that is unclear how often cladribine treatment will be re-initiated, and the total dosing required over a person's lifetime, as re-initiation of therapy after year 4 has not yet been studied. The Committee considered the assumption that approximately 10% of people would require cladribine retreatment by year five after treatment initiation to be reasonable, however that it could also be lower than 10%.

10.22. The Committee considered it is currently unclear how many people would switch from other therapies onto cladribine if it were to be funded, but that registry data from sources such as MS-base might help inform the assumption.

Summary for assessment

10.23. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for cladribine 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 Advisory Committee's assessment at this time and may differ from that requested by the applicant.

Population	People with relapsing-remitting multiple sclerosis with an EDSS score of 0-6, who meet the 2017 McDonald criteria
Intervention	Oral cladribine 3.5 mg/kg body weight over two years administered as one treatment course of 1.75 mg/kg per year. Each treatment course consists of two treatment weeks at week 1 and week 5 of the respective treatment year. Each treatment week consists of four or five days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. ~10% of people will undergo retreatment by year 5.
Comparator(s) (NZ context)	Currently funded RRMS treatments likely to be displaced by cladribine. Treatments likely to be displaced are ocrelizumab, natalizumab, fingolimod, dimethyl fumarate and teriflunomide. The extent to which displacement occurs to be informed by registry data and/or international assessments. A volume-weighted average will be estimated for both costs and treatment efficacy.
Outcome(s)	• Similar annualised relapse rates (ARR) and confirmed disability worsening at 3/6 months (CDW-3 or CDW-6) to currently funded RRMS treatments. (noting that Samjoo et al. J Comp Eff Res 2020;9:1255-74 suggests cladribine may possibly be more efficacious than some funded DMTs such as teriflunomide but less so than ocrelizumab and natalizumab, but that this is based on trends only so must be interpreted with caution). • Suitability benefits due to infrequent oral administration. • Reduced infusion burden on the health system due to some people switching from an infusion to an oral tablet.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

11. Memantine for the treatment of dementia

Application

11.1. The Advisory Committee reviewed two applications for the use of memantine (Ebixa) for the treatment of dementia. One application was received by a consumer for "'To aid in control of all Dementia symptoms including pain reduction and extend lucidity period", and the other was by a clinician applying for "Moderate dementia, but cholinesterase-inhibitors not tolerated".

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

Recommendation

11.1. The Advisory Committee recommended that the applications to list memantine for the treatment of dementia be **declined**.

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

- The health needs of those with dementia and their carers, which increase over time with the progression and severity of the disease.

- The variable strength and quality of evidence for the limited health benefit of memantine for the treatment of dementia.

- The suitability of memantine in comparison to currently funded treatments for dementia.

- The health-related cost and savings associated with listing memantine for dementia.

Discussion

Māori impact

11.3. The Committee discussed the impact of funding memantine for the treatment of dementia on Māori health outcomes. The Committee considered that although dementia is broadly considered a neurological condition, it can also be considered a mental health condition. Mental Health is one of Pharmac's five Hauora Arotahi (Māori health areas of focus).

11.4. The Committee noted that a recent study reported Māori experienced higher crude prevalence of dementia for each of the 4 years between July 2016 and June 2020 compared to Europeans in New Zealand (Cheung et al. BMJ Open. 2022;12:e062304). The Committee noted increased incidence in Māori in New Zealand echoed increased prevalence and incidence of dementia among indigenous populations internationally (Warren et al. Int Psychogeriatr. 2015;27:1959-70). The Committee noted that Māori are presenting to New Zealand memory services at younger ages than New Zealand Europeans (Warren et al. Int Psychogeriatr. 2015;27:1959-70).

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

11.5. The Committee noted the possible impact of funding memantine for the treatment of dementia disease on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted reported dementia prevalence in Pacific Islanders being 58%–70% higher in the age 60+ years population and 49%–63% higher in the 80+ population compared with Europeans (Cheung et al. BMJ Open. 2022;12:e062304). The Committee noted reporting that Pacific peoples tended to present with more advanced dementia (OR = 1.63, 95% CI: 0.98-2.70, P = 0.06) after adjustment for age and gender and were presenting to memory services approximately 5 years younger than New Zealand European people (Callum et al. Int J Geriatr Psychiatry. 2018;33:1098-104).

Background

11.6. The Committee noted an application for memantine for moderate to severe Alzheimer's Disease was recommended for decline by PTAC in August 2004, with PTAC considering the therapeutic effects of memantine to be similar to acetylcholinesterase inhibitors.

11.7. The Committee noted another application for memantine, for severe behavioural disturbances in moderate to severe dementia, was recommended for decline by PTAC in February 2008. The Committee noted PTAC considered that the evidence in support of memantine for the treatment of severe behavioural disturbance in patients with moderate to severe dementia was limited and that updated evidence supporting the efficacy of acetylcholinesterase inhibitors was stronger.

11.8. The Committee noted that subsequently in May 2010 Pharmac published a notification to decline both of the above applications alongside declining to approve funding of donepezil hydrochloride (an acetylcholinesterase inhibitor) for the treatment of Alzheimer's disease and other types of dementia.

Health need

11.9. The Committee noted the World Health Organization defines dementia as a term which describes several diseases that affect memory, thinking, and the ability to perform daily activities, and is a syndrome that can be caused by a number of diseases which over time destroy nerve cells and damage the brain, typically leading to deterioration in cognitive function (ie the ability to process thought) beyond what might be expected from the usual consequences of biological ageing. The Committee noted the impairment in cognitive function is commonly accompanied, and occasionally preceded, by changes in mood, emotional control, behaviour, or motivation.

11.10. The Committee noted that Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases (Duong et al. Can Pharm J(Ott), 2017;150:118-29). The Committee noted other forms include vascular dementia, dementia with Lewy bodies (abnormal deposits of protein inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal and temporal lobes of the brain). The Committee considered that often people may present with overlapping signs and/or symptoms of more than one subtype of dementia, and diagnosis is not always specified by and confined to a singular subtype.

11.11. The Committee noted that the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were widely used to screen for cognitive impairment in the past (Press et al. UpToDate. 2021). However, since 2020 the Mini-Addenbrooke's Cognitive Examination (M-ACE) has been the recommended screening tool for cognitive impairment in New Zealand. The Committee noted that the assessment of severity differs between the MMSE and MoCA, and M-ACE.

11.12. The Committee considered that dementia is likely under-diagnosed, and therefore under-reported in New Zealand. The Committee noted a recent population-based descriptive study utilised routinely collected health data from Statistics New Zealand to estimate the 1-year period prevalence for diagnosed dementia for each of the 4 years between July 2016 and June 2020 in the age 60+ years and age 80+ years populations and for four ethnic groups (Māori, Pacific Islander, NZ European, and Asian (Cheung et al. BMJ Open. 2022;12:e062304). The Committee noted the crude diagnosed-dementia prevalence was 3.8%–4.0% in the age 60+ population and 13.7%–14.4% in the age 80+ population across a four-year study period. The Committee noted that Māori and Pacific Islanders had higher crude prevalence than NZ Europeans in each of the 5-year age bands from age 60 to 95+ across the 4-year study period, while Asian people had lower crude prevalence than Europeans in each of the 5-year age bands from age 60 to 89 years across the four-year study period. The Committee considered that the true dementia prevalence in New Zealand is likely to be higher than that reported by this study due to the reliance on readily available data only. The Committee noted increased incidence in Māori in New Zealand echoes increased prevalence and incidence of dementia among indigenous populations internationally (Warren et al. Int Psychogeriatr. 2015;27:1959-70).

11.13. The Committee noted data collected from memory services in South Auckland reported that Māori presented to a NZ memory service at a younger age (mean age: 70.2, SD 7.6) than New Zealand Europeans (mean age: 79.2, SD 7.4), and after adjustment for gender and dementia subtype, Māori were 8.5 years younger than NZ European patients ($P < 0.0001$) (Callum et al. Int J Geriatr Psychiatry. 2018;33:1098-104).

11.14. The Committee noted dispensing numbers and estimated patient numbers provided for currently funded acetylcholinesterase inhibitors (donepezil tablets and rivastigmine patches), and considered that not all people with dementia are accessing or requiring treatment.

11.15. The Committee considered that people with dementia experience increasing health needs relating to and impacting quality of life over time as the disease progresses (Crowell et al. BMC Neurol. 2023;23:302). The Committee considered these needs relate to increasing cognitive impairment, required assistance with activities of daily living, and impacts of dementia on behaviour and mood. The Committee noted that relative all-cause mortality risk increases with Alzheimer's disease severity, more so if symptom onset occurs at a younger age (Crowell et al. 2023)

11.16. The Committee considered the health need for carers for people with dementia, noting a cross-sectional study on 'Caregiving burnout of community-dwelling people with dementia in Hong Kong and New Zealand' involving 16,725 care recipients (predominantly NZ European) in New Zealand from 2013 to 2016 (Chan et al. BMC Geriatr. 2021;21:261), which reported caregiver burnout was present in 13.9% of the New Zealand sample.

Health benefit

11.17. The Committee noted memantine is an antagonist of the NMDA (N-Methyl-D-Aspartate)-receptor subtype of the glutamate receptor which is used to slow the neurotoxicity thought to be involved in dementia and other neurodegenerative diseases.

11.18. The Committee noted memantine (Ebixa) is approved by Medsafe for "treatment of the symptoms of moderate to severe Alzheimer's disease".

11.19. The Committee noted that currently available evidence for the efficacy and safety of memantine assessed changes in cognitive and behavioural function, quality of life, and global rating assessments. The Committee noted no available evidence was identified for the associations of memantine with mortality or institutional care.

11.20. The Committee noted the Cochrane Systematic review of double-blind, parallel group, placebo-controlled, randomised trials of memantine in people with dementia up to March 2018, which included almost 10,000 participants over 44 trials (McShane et al. Cochrane Database Syst Rev. 2019;3:CD003154). The Committee considered the results of the review showed high-certainty evidence in around 3700 participants that memantine exhibited a small clinical benefit over placebo in the treatment of moderate-severe Alzheimer's disease. The Committee considered for mild Alzheimer's disease, mainly moderate-certainty evidence based on post-hoc subgroups from up to four studies in around 600 participants suggested probably no difference between memantine and placebo for cognitive function, activities of daily living, or behaviour and mood. Regarding the efficacy of memantine for vascular dementia, the Committee noted Cochrane review results of moderate- and low-certainty evidence from two studies in around 750 participants indicated probably a small clinical benefit derived from memantine for cognitive function, and possible small clinical benefit or behaviour and mood, probably no difference in clinical global ratings, and possibly no difference in activities of daily living. The Committee noted the Cochrane review's conclusion that there is high-certainty evidence showing no difference between memantine and placebo in the proportion of users experiencing at least one adverse event, and high-certainty evidence of no difference in falls.

11.21. The Committee noted results from a systematic review and individual patient data indirect comparison network meta-analysis (NMA) which assessed 80 randomised controlled trials involving 21,138 people, and a subset of 12 randomised controlled trials with individual patient data involving 6906 people, which examined the comparative efficacy and safety by patient characteristics of cognitive enhancers for managing Alzheimer's disease (Veroniki et al. BMJ Open. 2022;12:e053012). The Committee noted donepezil +memantine had the highest likelihood of being the most effective in improving MMSE scores. However the Committee considered the use of MMSE scores to be limited as a surrogate marker of disease effects, as it does not evaluate improvements in activities of

daily living, or behaviour and mood. This was in addition to the Committee noting the limitations of indirect comparisons more generally.

11.22. The Committee noted results from an indirect comparison multiple treatment network comparison meta-analysis of 54 placebo-controlled trials of memantine and donepezil alone and in combination for Alzheimer's disease (Guo et al. Brain Behav. 2020;10:e01831). The Committee considered from the analysis it was unclear if memantine monotherapy provided clinical benefit, but noted that combination therapy reported a small but possibly clinically relevant improvement in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) (mean difference (MD) 5.01, 95% credible interval (95% CrI) 0.86 to 10.73), the Committee however again noting the limitations of indirect comparisons.

11.23. The Committee noted results of a systematic review and meta-analysis of 30 randomised controlled clinical trials assessing the effectiveness of pharmacological and non-pharmacological treatments for people living with severe dementia (Profyri et al. Ageing Res Rev. 2022;82:101758). The Committee noted only two trials included in the study included memantine, and considered the analysis indicated memantine having very small clinical benefit, the Committee additionally reiterating the limitations of indirect comparisons.

11.24. The Committee noted results from a meta-analysis of nine randomised controlled trials (2433 participants) of memantine monotherapy for Alzheimer's disease (2 studies in mild disease, and 7 in moderate-severe disease) (Matsunaga e al. PLoS One. 2015;10:e0123289). The Committee considered the analysis indicated memantine having small beneficial clinical effects on cognition, behaviour, activities of daily living, and global function.

11.25. The Committee noted results of a systematic review of cognitive test accuracy studies and biomarker accuracy studies, and trials of Alzheimer's dementia treatment to March 2019 (Fink et al. Agency for Healthcare Research and Quality (US); 2020. Report No.: 20-EHC003). The Committee noted six trials were included, which assessed the efficacy of memantine in comparison to placebo (2 trials n mild-moderate dementia, 4 in moderate-severe dementia). The Committee noted that one trial compared memantine monotherapy to placebo, and results reported no difference in function, insufficient evidence for differences in cognition, and a small improvement in clinical impression of change when comparing memantine with placebo. The Committee noted that five trials, with low strength of evidence, reported a small improvement in clinical impression of change for combination therapy (memantine + anticholinesterase inhibitor) but no change in function.

11.26. The Committee considered that overall, the strength of evidence for memantine for dementia is variable, including many small studies over limited durations. The Committee considered evidence showed small mean clinical improvements in those treated with memantine for moderate to severe Alzheimer's disease, but considered there was variability in improvement, and it is difficult to predict who will benefit most from treatment. The Committee considered the strength of evidence for memantine in vascular dementia to be of low to moderate certainty and indicating little treatment benefit.

Suitability

11.27. The Committee did not note any suitability benefits or concerns in comparison to the currently funded donepezil hydrochloride tablets.

Cost and savings

11.28. The Committee considered it reasonable to assume approximately 70% of dementia in New Zealand is Alzheimer's disease, and 10% of Alzheimer's disease to be severe

(Brookmeyer et al, Alzheimer's & Dementia. 2011;7:61-73, Gungabissoon et al, BMJ. 2020; 10: e035779). The Committee considered it reasonable to assume approximately 20% of dementia in New Zealand is vascular dementia, 90% of which is of mild to moderate severity.

11.29. The committee considered the evidence used to predict the population numbers who may receive memantine was reasonable.

11.30. The committee considered that memantine is likely to be utilised in combination with donepezil hydrochloride in severe Alzheimer's.

11.31. The committee noted the reviewed evidence suggested memantine may provide small improvements as monotherapy over donepezil and rivastigmine in some measured outcome areas, but the evidence is of variable certainty. The committee considered that, with respect to the evidence for memantine in vascular dementia, it was not a suitable condition to be included in the PICO.

11.32. The committee considered that a 6-month follow up appointment, to assess the efficacy of memantine in individuals, would be required.

Summary for assessment

11.33. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for [the pharmaceutical] 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.

Population	People with Alzheimer's dementia with either an MMSE score 10 to 18, or MoCA 4 to 11, or CDR of 2, or M-ACE equivalent, and are intolerant or contraindicated to donepezil tablets and/or rivastigmine patches. People with severe dementia and MMSE <10 or MCA <4 or CDR of 3 or M-ACE equivalent.
Intervention	Memantine hydrochloride at an initial daily dose of 5 mg in the first week, 10 mg in the second week, 15 mg in the third week. From week four, memantine is administered at a maintenance dose of 20 mg per day.
Comparator(s) (NZ context)	Possible comparators: • best supportive care (all populations) • rivastigmine transdermal patches (moderate Alzheimer's dementia and mild to moderate vascular dementia) • donepezil (moderate and severe Alzheimer's dementia)

Outcome(s)	Evidence indicates memantine may:
	• improve
	  • cognitive function
	  • performance of activities of daily living
	  • behaviour and mood
	  • health related quality of life
	• delay hospitalisation for dementia care
	• reduce adverse effects experienced with rivastigmine or donepezil

Table definitions:

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

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

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

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

12. Belimumab for the treatment of active lupus nephritis

Application

12.1. The Advisory Committee reviewed belimumab for the treatment of active lupus nephritis.

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

Recommendation

12.3. The Advisory Committee **recommended** that the subcutaneous formulation of belimumab for the treatment of active lupus nephritis be funded with a **high priority** within the context of treatment of renal disease subject to the following Special Authority criteria:

> **Initial application – (lupus nephritis)** only from any relevant practitioner on the recommendation of a relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria: All of the following:
> 1. The patient has lupus nephritis class III (focal lupus nephritis) or IV (diffuse lupus nephritis), with or without coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within 6 months of initiating treatment with belimumab; and
> 2. Patient must have started standard induction therapy (defined as corticosteroids with either cyclophosphamide or mycophenolate mofetil or other forms of mycophenolate) within the previous 60 days; and
> 3. Patient's disease has not progressed whilst on both cyclophosphamide and mycophenolate mofetil (or other forms of mycophenolate) induction therapies; and
> 4. Patient has an eGFR > 30mL/min/ 1.73m^2.

Renewal application – (lupus nephritis) only from any relevant practitioner on the recommendation of a relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Reduction in prednisone equivalents to ≤ 7.5 mg/day after 12 months of therapy
2. Patient has an estimated eGFR that is no more than 20% below the value before the renal flare (preflare value) or ≥ 60 mL/min/1.73 m2 after 12 months of therapy.

12.4. The Advisory Committee considered the following when making its recommendation:

- The health equity for Māori who are disproportionally affected by lupus nephritis class III and IV, and are less likely to find a match for kidney transplant
- The suitability of a subcutaneous formulation, that would allow individuals to administer the treatment themselves, after training
- The health benefit for individuals with lupus nephritis
- The gain in health-related quality of life for individuals with lupus nephritis
- The cost savings for the health system from a reduction in treatments for chronic kidney disease and transplantation
- A reduction in the need for steroid and cyclophosphamide use

12.5. The Advisory Committee recommended the Nephrology Advisory Committee review the PICO and the Special Authority criteria, particularly the need for a biopsy to confirm diagnosis, and the age criteria.

Discussion

Māori impact

12.6. The Committee discussed the impact of funding belimumab for the treatment of lupus nephritis (LN) on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes. The Committee noted that systemic lupus erythematosus (SLE) and LN are not part of the Hauora Arotahi.

12.7. The Committee noted Māori are disproportionally affected by LN, less likely to be appropriately managed on current therapeutic regimens due to practical healthcare barriers, and experience higher rates of end stage renal disease and mortality (Concannon et al. Lupus. 2022;31:1671-78).

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

12.8. The Committee discussed the impact of funding belimumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted a New Zealand-based lupus study that reported a threefold increased risk of LN amongst Pacific peoples compared to New Zealanders of European descent (Burling et al.2007), as well as an increase in incidence of end stage renal failure compared to other New Zealanders (Stewart et al. Nephrol Dial Transplant. 2004;19:678-85).

Background

12.9. The Committee noted the Nephrology Advisory Committee did not formally review the belimumab application at its meeting in March 2023, but did provide some early thoughts ahead of its formal review.

Health need

12.10. The Committee previously noted the health need of people with systemic lupus erythematosus (SLE) in November 2012.

12.11. The Committee noted the mortality rate in LN is highest in individuals with class III and class IV LN, due to the higher risk of progressive chronic kidney disease (CKD) and ultimately end-stage kidney disease (ESKD).

12.12. The Committee noted not all individuals with LN had a renal biopsy undertaken, unless class III or IV was suspected.

12.13. The Committee noted the Concannon et al. 2022 study of children in New Zealand diagnosed with LN between 1992 and 2018. The Committee noted 42 children had LN of which 33 had class III or IV. The Committee noted there was a total of 12 Māori and 18 Pacific individuals included in the study, of which 23 had Class III or IV LN. The Committee noted the study reported 11 developed ESKD at mean age of 18 years (of which 10 were Māori or of Pacific ethnicity). The Committee noted eight individuals had died by the end of the study, with an average age of death of 23 years. The Committee considered Māori and Pacific peoples were disproportionally affected by LN.

12.14. The Committee noted that whilst the overall incidence of LN in New Zealand was consistent with global estimates, Māori were more likely to present with severe disease (Class II-V) and more likely to progress to CKD and ESKD due to LN (Ly et al. Lupus. 2017;26:893-97)

12.15. The Committee noted a New Zealand lupus study that reported a threefold increased risk of LN amongst Pacific peoples compared to New Zealanders of European descent (Burling et al.2007).

12.16. The Committee also noted Stewart et al. Nephrol Dial Transplant. 2004;19:678-85, which reported an incidence of ESKD due to LN as 13.2 per million for Pacific peoples compared to 1.2 for other New Zealanders.

12.17. The Committee noted Petri et al. J Rheumatol. 2021; 48:222–7, a cohort study of all those with LN reported the risk of renal failure to be 2.7% (95% CI 2.1–3.5%) within 5 years, 4.8% (95% CI 4.0–5.9%) within 10 years, and 8.4% (95% CI 7.0–10.0%) within 20 years of SLE diagnosis.

12.18. The Committee noted the Improving Global Outcomes (KDIGO) 2023 Clinical Practice Guideline for Lupus Nephritis published in March 2023, which provided clinical practice guidelines for the management of LN.

12.19. The Committee noted that dual or triple immunosuppression with combinations of steroids, mycophenolate azathioprine, cyclosporin or tacrolimus were common as maintenance therapy in New Zealand. The Committee considered these had modest efficacy in treating LN.

12.20. The Committee considered anecdotally that, with current treatment, renal response is about 25% after 6 months of treatment, which is significantly less than clinically required.

Health benefit

12.21. The Committee noted a study by Yapa et al. Lupus. 2016;25:1448-55 that reported levels of belimumab were stable at four weeks in those with SLE. The Committee considered the subcutaneous formulation would likely be non-inferior to the intravenous formulation for health benefit, given the comparable average drug concentrations after intravenous and subcutaneous dosing.

12.22. The Committee noted the BLISS-LN trial, a phase 3, multinational, multicentre randomised, double-blind, placebo-controlled in 448 with LN. The Committee noted the following published or presented results:

12.22.1. Furie et al. N Engl J Med. 2020;383:1117-28 reported results at 104 weeks:

- Significantly more in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs. 32%; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; P = 0.03) and a complete renal response (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P = 0.02).

- The risk of a renal-related event or death was lower for belimumab than placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P = 0.001). The Committee noted the majority of these events were an increase in proteinuria, or other kidney disease-related treatment failure.

- The safety profile of belimumab was consistent with that in previous trials.

12.22.2. A poster presented by Furie et al at EULAR 2021 reported the 6-month results from an open label (OL) extension (of BLISS-LN) where 123 individuals switched from placebo-to belimumab, and 132 remained on belimumab:

- The proportion who attained Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score <4 decreased slightly from OL baseline to OL Week 28 in the placebo to belimumab group and increased slightly in the belimumab-to-belimumab group.

- Among those receiving average daily prednisone-equivalent doses of ≤5 mg/day, ≤7.5 mg/day or ≤10 mg/day, the dose was maintained from open label baseline to open label week 28.

12.22.3. Furie et al. CJASN 2022,17: 1620–30 reported the 28-week results from the OL extension (of BLISS-LN):

- From OL baseline to week 28, increases occurred in the proportions achieving primary efficacy renal response (placebo-to-belimumab: from 60% to 67%; belimumab-to-belimumab: from 70% to 75%) and complete renal response (placebo-to-belimumab: from 36% to 48%; belimumab-to-belimumab: from 48% to 62%).

- Based on double-blind phase criteria, changes also occurred in the proportions achieving primary efficacy renal response (placebo-to-belimumab: from 54% to 53%; belimumab-to-belimumab: from 66% to 52%) and complete renal response (placebo-to-belimumab: from 34% to 35%; belimumab-to-belimumab: from 46% to 41%).

- The seeming decrease in response rates in the belimumab-to-belimumab groups was attributed to discontinuations/administration of glucocorticoids for non-SLE reasons as opposed to nephritis.

12.23. The Committee made the following observations and comments relating to BLISS-LN:

12.23.1. The Committee noted the low number of individuals randomised in the study.

12.23.2. The Committee noted the choice of combination treatment in the trial was physicians' choice, however, there was a significant preference for mycophenolate mofetil. The Committee noted that this was part of the standard of care treatment in New Zealand.

12.23.3. The Committee noted a high discontinuance rate, with approximately one third of people who discontinued belimumab due to adverse events or lack of efficacy. The Committee considered there was no signal of an excess number of adverse events from belimumab relative to placebo.

12.23.4. The Committee considered when evaluating the primary endpoint of primary efficacy renal response, a relatively low percentage of individuals entered remission, however the effect was maintained over a two-year period.

12.23.5. The Committee noted for renal related events, the study length was not sufficient to evaluate if belimumab affected death or progression to ESKD. The Committee noted Dall'Era et al. Arthritis Rheumatol 2015; 67:1305-13, which reported if an individual's proteinuria can be kept at below 0.8g/day this may slow progression to ESRD.

12.23.6. The Committee noted the biggest change in parameters was for reduction in proteinuria. The Committee considered proteinuria a good prognostic marker for ESKD.

12.23.7. The Committee noted the results in the OL extension study were difficult to compare to the initial trial, as the changes in EGFR were compared to those at the start of the OL extension rather than the start of the initial trial.

12.23.8. The Committee noted Anders et al. Nephrol Dial Transplant. 2023:gfad167, which reported the best clinical response were observed in individuals whose disease had relapsed rather than those who were newly diagnosed with LN. The Committee therefore considered it appropriate that belimumab be used as a second line treatment.

12.23.9. The Committee considered those whose disease relapsed in the trial on belimumab treatment had an increased time to kidney related event.

12.23.10. The Committee noted the lack of data collected in trials regarding health-related quality of life when administered belimumab, and that this is an important parameter to measure. The Committee noted that while not reported in the trials, those who had active disease would have had a worse quality of life compared to non-active disease.

12.23.11. The Committee noted that cyclophosphamide affects fertility and therefore a reduction in use would be of benefit for people intending to have child.

12.24. The Committee noted Strand et al. Arthritis Care Res (Hoboken). 2019;71:829-38, which reported the effect of belimumab in those with SLE. The study reported an improvement in fatigue scores and Short Form 36 (SF-36) health survey physical and mental component summary scores. The Committee considered this was a significant improvement that was sustained over time.

12.25. The Committee noted Wallace et al. Arthritis Rheumatol. 2019;71:1125-34, a long term follow up study of belimumab for up to 13 years in individuals with SLE reporting the following results:

- The proportion of individuals experiencing an SLE Responder Index (SRI) response increased from 32,8% in year one to 75.6% of those remaining on treatment at year 12.

- The glucocorticoid dose was decreased in people who had been receiving >7.5 mg/day at baseline.

12.26. The Committee noted the following studies:

- Dooley et al. Lupus, 2013 22: 63-72
- Blair et al. Drugs. 2018;78:355-66
- Rovin et al. Kidney Int. 2022;101:403-13
- Yu et al. Am J Kidney Dis. 2023;8:294-306.e1
- Atisha-Fregoso et al. Arthritis Rheumatol. 2021;73:121-31
- Lee et al. Pharmacology. 2023;108:17-26
- Lee et al. Lupus. 2022 Oct; 31:1468-76
- Chen et al. J Clin Rheumatol. 2023 Mar;29:95-100.
- Zhang et al. Ren Fail. 2023;45:2207671
- Zhang et al. Immun Inflamm Dis. 2023;11:e954.
- Ramachandran et al. J Comp Eff Res. 2018;7:581-93

Suitability

12.27. The Committee noted as a maintenance therapy the subcutaneous formulation is useful for individuals to be able to self-administer, following relevant training. The Committee considered that an intravenous formulation would not be suitable for maintenance therapy due to the inconvenience of an individual having to regularly travel to an infusion service, and also in light of the additional demand that would be placed on an already overburdened system. The Committee considered if an intravenous formulation were funded, the uptake would be low.

Cost and savings

12.28. The Committee considered treatment with belimumab would likely result in a reduction in steroid use, as part of the treatment protocol. The Committee considered steroid free treatment would provide a long-term health benefit.

12.29. The Committee noted that lupus flares require intensive treatment by practitioners in both a community and hospital setting (Bell CF et al. Lupus 2022;32:301-9). The Committee noted this has significant associated costs.

12.30. The Committee considered that there is likely to be less than the predicted 89 individuals with LN class III and IV. The Committee considered there may be some individuals with class V who may benefit from treatment.

12.31. The Committee considered individuals whose disease is challenging to treat with a triple immunosuppressant regime would gain the most health benefit from belimumab.

12.32. The Committee noted that specialist training is required to administer some of the current cytotoxic treatments, and therefore access can be affected if there is not a qualified member of staff to administer the treatment.

12.33. The Committee considered that belimumab treatment would be received on an ongoing basis to prevent relapse. The Committee considered the maintenance therapy may be ongoing, possibly between 5-15 years.

Funding criteria

12.34. The Committee noted that LN also affects children, who would most likely have the disease for longest and have the most chance of progressing to ESKD. The Committee

noted that there is some data being generated in a paediatric population (eg. PLUTO trial).

12.35. The Committee noted that not all individuals would have a biopsy to confirm disease. The Committee considered a biopsy is the gold standard for diagnosis. The Committee noted that as access to a biopsy was not universal in New Zealand it should not be included in the Special Authority criteria, to support equitable access to belimumab.

12.36. The Committee considered belimumab would be most appropriate to use in individuals after the failure of two immunosuppressive agents.

12.37. The Advisory Committee requested the Nephrology Advisory Committee review the Special Authority criteria, particularly the need for a biopsy to confirm diagnosis, and the age criteria.

Summary for assessment

12.38. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for belimumab if it were to be funded in New Zealand for lupus nephritis. 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 diagnosed with SLE and active, lupus nephritis Class III-V, who have experienced treatment failure after trialling two immunosuppressive agents.
Intervention	Subcutaneous injection: 400-mg dose (two 200-mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter.
Comparator(s)	Belimumab would be an add-on therapy to current treatment. Corticosteroid use may be reduced for some people.
Outcome(s)	• Reduction in renal flares - Reduction in symptoms associated with active LN, eg. fatigue, joint tenderness - reduction in health system costs associated with renal flares • Response to treatment may delay the progression to kidney disease. • Reduction in corticosteroid use - reduction in the adverse effects associated with high corticosteroid use.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

12.39. The Advisory Committee requested the Nephrology Advisory Committee review the PICO particularly the age criteria, and confirmation of disease via a biopsy.