PHARMAC
TE PĀTAKA WHAIORANGA

Pharmacology and Therapeutics Advisory Committee
Objective advice to Pharmac

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 14 November & 15 November 2024

1. Present:

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

Observer:
Hon. Paula Bennett (Pharmac Board Chair) – part of meeting

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

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

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

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

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

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

3. Summary of Recommendations

	Pharmaceutical and Indication	**Recommendation**
8.4	Widening access to ferric carboxymaltose for people with heart failure with reduced ejection fraction who are iron deficient without anaemia	Low Priority
8.5	Widening access to ferric carboxymaltose for people with heart failure with mid-range ejection fraction who are iron deficient without anaemia	Low Priority
8.6	Widening access to ferric carboxymaltose for all people with heart failure who are iron deficient without anaemia	Decline
9.3	Tezepelumab for first-line biologic treatment of severe uncontrolled asthma, subject to Special Authority criteria	High Priority
10.3	Testosterone 1% w/v cream (AndroFeme 1) for the treatment of hypoactive sexual desire dysfunction in post-menopausal women	Declined
11.3	Subcutaneous ocrelizumab for the treatment of the same indications as the intravenous formulation (relapsing remitting multiple sclerosis, and primary progressive multiple sclerosis), subject to Special Authority criteria.	High Priority
12.4	Widening access to benralizumab and mepolizumab to allow second-line treatment in	High Priority

	patients with severe eosinophilic asthma, subject to Special Authority criteria	
13.3	Atezolizumab (with chemotherapy) for the treatment of advanced or metastatic triple negative breast cancer with a PD-L1 expression over 1%	Declined

4. Record of PTAC meeting held 16 August

4.1. The Committee reviewed the record of the PTAC meeting held on 16 August

4.2. The Committee accepted the record.

5. Action Points

5.1. There are no current action points.

6. Pharmac Update

6.1. The Committee noted the Pharmac Update.

6.2. The Committee and Pharmac staff acknowledged this will be the final meeting for Dr Jane Thomas as Chair of PTAC. Everyone thanked and acknowledged Dr Thomas for her significant contribution to PTAC and Pharmac's work over the last 12 years, the last 3 years as PTAC Chair.

7. Specialist Advisory Committee Record

May 2024 Rare Disorders Specialist Advisory Committee

7.1. PTAC reviewed the records of the Rare Disorders Advisory Committee meeting held on 29 May 2024.

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

June 2024 Anti-Infectives Specialist Advisory Committee

7.3. PTAC reviewed the records of the Anti-Infectives Specialist Advisory Committee held on 13 June 2024.

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

July 2024 Rare Disorders Specialist Advisory Committee

7.5. PTAC reviewed the records of the Rare Disorders Advisory Committee ad-hoc meeting held on 27 August 2024.

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

July 2024 Cancer Treatments Specialist Advisory Committee

7.7. PTAC reviewed the records of the Cancer Treatments Advisory Committee meeting held on 12 July 2024.

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

8. Correspondence: Ferric carboxymaltose – widening access for people with heart failure who are iron deficient without anaemia

Application

8.1. The Committee reviewed ferric carboxymaltose for the treatment of people with heart failure who are iron deficient without anaemia.

8.2. The Committee noted that Pharmac had received feedback in response to a consultation for the funding of ferric carboxymaltose for iron deficiency anaemia in people with chronic inflammatory disease. Clinicians noted an unmet health need in individuals with heart failure who are iron deficient without anaemia.

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

Recommendations

8.4. The Committee **recommended** that widening access to ferric carboxymaltose for people with heart failure with reduced ejection fraction who are iron deficient without anaemia be funded with a **low priority**.

8.5. The Committee **recommended** that widening access to ferric carboxymaltose for people with heart failure with mid-range ejection fraction who are iron deficient without anaemia be funded with a **low priority**.

8.6. The Committee **recommended** that widening access to ferric carboxymaltose for all people with heart failure who are iron deficient without anaemia be **declined**.

8.7. In making this recommendation the Committee:

8.7.1. recognised the high health need of people with heart failure, and the unmet health need of individuals from the currently available treatments

8.7.2. noted the evidence that treatment with ferric carboxymaltose provides a health benefit in reducing the number of heart failure related hospitalisations. The Committee took into account the current resource constraints in the health system at the time of making the recommendation

8.7.3. noted that Māori and Pacific people are disproportionately impacted by heart failure compared with other ethnic groups in Aotearoa New Zealand.

Discussion

Māori impact

8.8. The Committee discussed the impact of widening access to ferric carboxymaltose for the treatment of people with heart failure who are iron deficient without anaemia on Māori health areas of focus and Māori health outcomes. The Committee noted it had previously considered the health need of individuals with heart failure in February 2022. The Committee noted in 2022 that heart failure mortality rate among Māori was more than twice as high as that of non-Māori (RR 2.36; confidence interval CIs 1.76 to 3.17), with heart failure hospitalisation rates for Māori being about 4 times that of non-Māori (RR 4.01; CI 3.83 to 4.21) (New Zealand Ministry of Health: Health Status Indicators. 2018). The Committee considered the cause for the disproportionate prevalence and impact of heart failure in Māori is multifaceted, and that key contributing factors may include socioeconomic factors, barriers in access to health care, exposures (for example smoking, nutrition, alcohol, exercise), and the presence of comorbidities (for example hypertension, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, psychiatric disorders) (New Zealand Ministry of Health: Ngā tauwehe tūpono me te marumaru: Risk and protective factors. 2021). The Committee also noted that heart failure falls into the Pharmac Māori health area of focus *Manawa Ora* | Heart Health, which encompasses high blood pressure, and stroke but also considers other cardiac conditions such as heart failure.

Populations with high health needs

8.9. The Committee discussed the health need(s) of people with heart failure who are iron deficient without anaemia among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the

impact of funding treatments for people with heart failure who are iron deficient without anaemia.

8.10. The Committee previously noted the health need of Pacific people with heart failure in May 2023. The Committee noted that Pacific people are more than twice as likely to be hospitalised for heart failure compared to non-Māori, non-Pacific people and that Pacific people face barriers, and experience treatment gaps, when accessing appropriate healthcare to address their cardiovascular health needs.

Background

8.11. The Committee noted that Pharmac received feedback from health professionals working in cardiology services in response to a consultation for the funding of ferric carboxymaltose for iron deficiency anaemia in people with chronic inflammatory disease. The clinicians noted there was an unmet health need for individuals with heart failure who are iron deficient without anaemia and would not be eligible for access under the proposed Special Authority criteria. Pharmac sought advice on the unmet health need of this population and the health benefit of ferric carboxymaltose treatment of this group.

Health need

8.12. The Committee noted it had previously considered the health need of individuals with heart failure in February 2022 and May 2023.

8.13. The Committee noted individuals with heart failure that experience anaemia (defined as a haemoglobin value of less than 13.5 gm/dl in a man or less than 12.0 gm/dl in a woman, with a serum ferritin level of less than or equal to 20 mcg/L) can access ferric carboxymaltose under the current Special Authority criteria.

8.14. The Committee noted approximately 40% to 50% of people with chronic heart failure experience iron deficiency, with the prevalence being higher in individuals with more severe disease, and New York Heart Association (NYHA) Class III and IV compared to those with NYHA Classes I and II. The Committee noted that the prevalence of iron deficiency increases and is seen in up to 80% of those presenting with acute heart failure to hospital. Iron deficiency has also been reported in heart failure with preserved ejection fraction cohorts, with a meta-analysis showing a prevalence of up to 59% (95% CI 52% to 65%) (Beale et al. Open Heart. 2019;6:e001012). Iron deficiency in heart failure is defined as serum ferritin ≤100 ng/mL, or between 100-300 ng/mL with low transferrin saturation (TSATs) under 20% (Martens et al. Circ Heart Fail. 2024;17:e011440).

8.15. The Committee noted anaemia and iron deficiency are common in people with heart failure and are associated with poor clinical status and worse outcomes (Anand et al. Circulation. 2018;138:80-98).

8.16. The Committee noted that iron deficiency, as well as reduced serum ferritin levels, have also been associated with reduced exercise tolerance. In people with heart failure and lower iron counts reduced peak oxygen consumption impairs exercise tolerance (despite a compensatory increase in respiratory rate) (Jankowska et al. J Card Fail. 2011;17:899-906).

8.17. In addition, the Committee noted low iron levels have also been associated with lower health-related quality of life, irrespective of anaemia status, than those with adequate iron storage supplies in an analysis of > 500 people with chronic heart failure (Comin-Colet et al. Eur J Heart Fail. 2013;15:1164-72).

8.18. The Committee noted the clinician feedback that estimated 25.5% of people treated for heart failure would require treatment with ferric carboxymaltose. The clinician feedback considered that the majority would have iron deficiency without anaemia.

8.19. The Committee considered that most individuals should be receiving the four-pillar treatment guideline directed care including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor/neprilysin inhibitor (ARNI), with a beta-blocker, a mineralocorticoid receptor

antagonist and sodium-glucose cotransporter-2 (SGLT2) inhibitor (Heidenreich et al.Circ. 2022;145:18: e895-e1032). The Committee noted that access to SGLT2 inhibitors is limited to individuals who can self-fund or who meet current Pharmac Special Authority criteria. The Committee noted that diuretics may be added to the treatment regime based on an individualised clinical assessment.

8.20. The Committee noted the clinician feedback that considered individuals under speciality services (secondary) care would be screened and prescribed intravenous iron, which is considered an off-label treatment. The clinician feedback considered that those not under specialty care would not receive intravenous iron, and many people found the current Special Authority criteria confusing.

8.21. The Committee noted the 2023 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure recommends the use of ferric carboxymaltose in people with heart failure with reduced ejection fraction or people with heart failure with mildly reduced ejection fraction, and iron deficiency, to improve symptoms and quality of life, and considered that treatment with ferric carboxymaltose reduced the risk of heart failure hospitalisation.

Health benefit

8.22. The Committee noted the following publications that reported the results of the CONFIRM HF, FAIR HF, and AFFIRM HF trials that investigated the effect of ferric carboxymaltose in individuals with heart failure with iron deficiency without anaemia:

- Anker et al. N Engl J Med. 2009;361:2436-48.
- Ponikowski et al. Eur Heart J. 2015;36:657-68
- Jankowska et al. Eur Heart J. 2021;42:3011-20

8.22.1. The Committee noted the CONFIRM-HF trial reported treatment with ferric carboxymaltose significantly extended the six-minute walk test (6MWT) distance at week 24 (difference versus placebo: 33 ± 11 m, P = 0.002) and was associated with a significant reduction in the risk of hospitalisations for worsening heart failure [hazard ratio (95% CI: 0.39 (0.19-0.82), P = 0.009].

8.22.2. The Committee noted the FAIR-HF trial reported significant improvements compared with placebo in the distance on the 6MWT and in the quality of life, as evaluated by the EQ-5D visual assessment score, and overall Kansas City Cardiomyopathy score, at weeks 4, 12, and 24 (P<0.001 for all comparisons). The rate of first hospitalisation for any cardiovascular reason among individuals receiving ferric carboxymaltose compared with placebo was not statistically significant (hazard ratio, 0.53; 95% CI, 0.25 to 1.09; P=0.08). The hazard ratio for death or first hospitalisation for any cardiovascular reason among individuals who received ferric carboxymaltose as compared with those who received placebo showed no significant difference (hazard ratio,0.61; 95% CI, 0.32 to 1.18; P=0.14).

8.22.3. The Committee noted the AFFIRM-HF trial reported treatment with ferric carboxymaltose, in people with or without anaemia, improved symptoms, functional capacity, and quality of life.

8.22.4. The Committee noted the duration of the three studies ranged from six to twelve months.

8.22.5. The Committee considered these studies all utilised the same definition of iron deficiency without anaemia and had similar dosing regimens.

8.22.6. The Committee noted these studies predominately recruited individuals with heart failure with reduced ejection failure, NYHA class II/III, with ejection fraction of <45%.

8.22.7. The Committee noted that the standard of care has substantially changed since these studies were performed.

8.22.8. The Committee considered that overall, these trials reported a reduction in heart failure admission rates, and improvement in quality of life.

8.23. The Committee noted Anker et al. Eur J Heart Fail. 2023;25:1080-90, which reported the results of a Bayesian meta-analysis of data from the FAIR-HF (n = 459), CONFIRM-HF (n = 304), AFFIRM-AHF (n = 1108) and IRONMAN (n=1137) trials. The study reported that compared with placebo, treatment with ferric carboxymaltose significantly reduced the rates of recurrent heart failure hospitalisations and cardiovascular mortality (RR 0.73, 95% credible interval [CI] 0.48-0.99; between-trial heterogeneity tau = 0.16). Whilst the study reported that treatment of individuals with heart failure with reduced ejection fraction with ferric carboxymaltose does appear to reduce a combined endpoint of cardiovascular mortality and heart failure hospitalisation. The Committee noted that Bayesian analyses suggest uncertainty is still present in subgroup analyses (age, sex, aetiology of heart failure, transferrin saturation, eGFR, haemoglobin, ferritin and NYHA class) as statistical power was lacking due to the smaller subgroup sizes.

8.24. The Committee noted the AFFIRM-AHF trial (Ponikowski et al. Lancet. 2020;396:1895-904) that evaluated the effect of ferric carboxymaltose in 1110 individuals with acute heart failure. The Committee noted that the authors concluded that treatment with ferric carboxymaltose reduced the risk of heart failure hospitalisations, with no apparent effect on the risk of cardiovascular death.

8.25. The Committee noted the IRONMAN trial (Kalra et al. Lancet. 2022 ;400:2199-209) that evaluated the effect of ferric derisomaltose, a different formulation of high-dose, intravenous iron, in 1137 individuals with heart failure with reduced ejection fraction (≤45%). The study reported that intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death. The Committee noted that at four months, those randomised to ferric derisomaltose had a better overall quality of life score and physical domain score on the Minnesota Living with Heart Failure questionnaire compared with those in the usual care group. There were no differences between the groups in these scores at 20 months, in the EQ-5D scores at 4 or 20 months, or in the 6MWT distance at 4 months.

8.25.1. The Committee noted that two different intravenous iron treatments were evaluated in the AFFIRM-AHF and IRONMAN trial.

8.25.2. The Committee noted that the AFFIRM-AHF trial had a longer duration of follow up than previous studies with a median follow up of 2.7 years.

8.25.3. The Committee considered the best supportive care in the AFFIRM-AHF and IRONMAN trial to be closer to the standard of care currently received in New Zealand.

8.25.4. The Committee noted that the COVID-19 pandemic interrupted collection of data in the IRONMAN study, therefore data was separated into pre-and post-pandemic stages.

8.25.5. The Committee noted that both studies reported a reduction in risk in heart failure hospitalisation however the AFFIRM-AHF trial reported no effect of iron treatment on the risk of cardiovascular death.

8.26. The Committee noted the Vukadinovic et al. Clin Res Cardiol. 2023;112:954-66 meta-analysis of the AFFIRM-AHF and IRONMAN studies. The Committee noted the study reported that ferric carboxymaltose or ferric derisomaltose reduces the composite risk of recurrent heart failure hospitalisations and cardiovascular death, while effects on cardiovascular death alone are indeterminate based on the available evidence.

8.27. The Committee noted a recent meta-analysis Ponikowski et al. Eur Heart J. 2023;44:5077-91 that included three trials (AFFIRM-AHF, CONFIRM AHF and HEART FID) with 4501 people with heart failure with reduced ejection fraction.

8.27.1. The analysis reported ferric carboxymaltose was associated with a significantly reduced risk of hospital admissions for heart failure and cardiovascular causes, with no apparent effect on mortality.

8.27.2. The Committee noted that the authors reported that it appeared that a higher cumulative dose of ferric carboxymaltose administered during the first 6 months of therapy (likely the result of re-dosing) may be associated with a slightly greater treatment effect after 6 months compared with a lower cumulative dose although, the treatment effect did not reach significance in either dose group.

8.27.3. The Committee also noted the authors reported the treatment effect following a single course of ferric carboxymaltose appeared to be absent >6 months after therapy.

8.28. The Committee noted the following studies:

- Mentz et al. N Engl J Med. 2023;389:975-86.
- Anker et al. N Engl J Med. 2009;361:2436-48
- Ponikowski et al. Eur Heart J. 2015;36:657-68
- Jankowska et al. Eur Heart J. 2021;42:3011-20
- Filippatos et al. Circulation. 2023;147:1640-53
- Filippatos et al. Eur J Heart Fail. 2013;15:1267-76
- Comin-Colet et al. Eur Heart J. 2013;34:30-8.
- Khan et al. ESC Heart Fail. 2020;7:3392-400
- Doughty et al. N Z Med J. 2024;137:93-99.

8.29. Overall, the Committee considered that there was robust trial evidence to support a health benefit from treatment with ferric carboxymaltose in individuals with either chronic or acute heart failure.

8.30. Overall, the Committee considered there was evidence to support the health benefit of ferric carboxymaltose in individuals with heart failure who had a reduced ejection fraction, however there were fewer data for people with mildly reduced ejection fraction, and insufficient data for people with preserved ejection fraction.

Suitability

8.31. The Committee noted that as an intravenously administered treatment, individuals would be required to travel to infusion services to receive treatment. The Committee noted the clinician feedback did suggest some individuals may receive treatment in a community setting outside of an infusion centre.

Cost and saving

8.32. The Committee considered that repeat dosing patterns for ferric carboxymaltose would be common in New Zealand, and it was reasonable to estimate these dosing patterns based on trial data.

8.33. The Committee noted approximately 60% of participants in the IRONMAN trial had more than one dose of ferric carboxymaltose, and meta-analysis data suggested a threshold of <1500 mg to equate to one dose. Therefore, the Committee considered it was likely that most people would receive on average at least 1500 mg of ferric carboxymaltose.

8.34. The Committee noted that ferric carboxymaltose reduced emergency department presentations and hospitalisations for heart failure, and this would represent a material saving to health sector budgets.

Summary for assessment

8.35. The Committee considered that the PICO table below reflected the intended population, intervention, comparator, and outcome, if ferric carboxymaltose were to be funded for iron deficiency in the setting of heart failure. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with heart failure with a left ventricular ejection fraction of less than 49%, with iron deficiency (without anaemia) • Iron deficiency defined by a ferritin below 100 lg/l irrespective of TSAT or a ferritin between 100 and 300 lg/l with a TSAT below 20% Anaemia defined as a haemoglobin level <12 g/dl in women and <13g/dl in men
Intervention	Ferric carboxymaltose IV - Expected target cumulative dose of 1500 mg (Ponikowski et al. Eur Heart J. 2023;44:5077-91)
Comparator(s) (NZ context)	No iron treatment
Outcome(s)	Improvement in health-related quality of life • FAIR-HF reported that participants receiving ferric carboxymaltose had higher EQ-5D VAS scores compared to those who received placebo at 24 weeks (mean difference = 7±2) (FAIR-HF; Anker et al. New Engl J Med. 2009;361: 2436-48) • This improvement in health-related quality of life is not durable and most studies report a waning of treatment effect, even with repeat dosing (Ponikowski et al. 2023). Reduction in risk of hospitalisation for heart failure • A meta-analysis reported that participants receiving ferric carboxymaltose had a lower rate of hospitalisation for heart failure compared to those who received placebo (HR = 0.84 [95% CI, 0.73 to 0.96]) (Ponikowski et al. 2023)
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. Tezepelumab (Tezspire) for severe uncontrolled asthma irrespective of phenotype

Application

9.1. The Committee reviewed the application from AstraZeneca Limited for tezepelumab for the treatment of severe uncontrolled asthma irrespective of phenotype. The Committee noted that Pharmac staff had clarified that the intent of the supplier application was for tezepelumab to be used as a first-line biologic.

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

Recommendation

9.3. The Committee **recommended** that tezepelumab be funded for first-line biologic treatment of severe uncontrolled asthma with a **high priority**, subject to the following Special Authority criteria:

TEZEPELUMAB
Initial application — Severe Uncontrolled Asthma
Applications only from a respiratory physician or clinical immunologist or any relevant practitioner on the recommendation of a respiratory physician or clinical immunologist. Approvals valid for 12 months.
All of the following:

1. Patient must be aged 12 years or older; and
2. Patient must have a diagnosis of severe uncontrolled asthma documented by a respiratory physician or clinical immunologist; and
3. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus a long-acting beta-2 agonist, or budesonide/formoterol as part of the anti-inflammatory reliever therapy plus maintenance regimen (SMART), unless contraindicated or not tolerated; and
4. Either:
   5.1. Patient has had at least four exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
   5.2. Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
5. Treatment is not to be used in combination with subsidised mepolizumab, benralizumab or omalizumab; and
6. Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be recorded; and
7. Patient has not previously received a biological therapy for their severe asthma.

Renewal — Severe Uncontrolled Asthma
Applications only from a respiratory physician or clinical immunologist or any relevant practitioner on the recommendation of a respiratory physician or clinical immunologist. Approvals valid for 2 years.
Both:

1. An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2. Either:
   2.1. Exacerbations have been reduced from baseline by 50% as a result of treatment with tezepelumab; or
   2.2. Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

9.4. In making this recommendation, the Committee considered:

9.4.1. tezepelumab provides a health benefit for the group with non-eosinophilic, non-allergic severe asthma phenotypes who have an unmet health need due to not being eligible for currently funded biologics

9.4.2. tezepelumab use would be associated with a reduction in hospitalisations due to reduced asthma exacerbations in this group, providing a benefit to the health system

9.4.3. funding tezepelumab would improve equity of access to biologics for people with asthma (for example access for those with non-allergic and non-eosinophilic phenotypes)

9.4.4. tezepelumab has similar suitability to existing biologics for severe uncontrolled asthma.

9.5. The Committee recommended the Respiratory Advisory Committee review the Special Authority criteria (including age criteria) and advise on the likely prescribers for, and potential length of time on, tezepelumab treatment, in addition to the likely sequencing of biologics for asthma if tezepelumab were to be funded.

9.6. The Committee considered all currently funded biologics for severe asthma should not be used in combination with other first-line biologics and the Special Authority for omalizumab should be amended to reflect this.

Discussion

Māori impact

9.7. The Committee discussed the impact of funding tezepelumab for the first-line biologic treatment of severe uncontrolled asthma, irrespective of phenotype on Māori health areas of focus and Māori health outcomes. The Committee noted respiratory health is a Pharmac | Te Pātaka Whaioranga Hauora Arotahi | Māori health area of focus. The Committee noted that the incidence of severe asthma events (such as hospitalisations) is much higher in Māori than non-Māori, and there are similar epidemiologic features in other populations with high health needs and/or experiencing health inequity (Chan et al. Respir Med. 2023:217:107365). Over 50% of all hospital admissions in Aotearoa New Zealand for asthma were experienced by Māori and Pacific asthmatics in both 2010 and 2019 despite these two ethnic groups comprising only 25% of the total asthma population (Chan et al. 2023).

Populations with high health needs

9.8. The Committee discussed the health needs of people with severe uncontrolled asthma irrespective of phenotype among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding tezepelumab and considered:

9.8.1. Asthma prevalence increases with increasing socioeconomic deprivation status. The Committee also noted higher rates of asthma exacerbations, and morbidity associated with deprivation (Chan et al.2023).

9.8.2. After adjustment for age, sex, and deprivation, the highest level of asthma exacerbations are among Pacific peoples. Hospitalisation rates for asthma are more than three times higher for Pacific peoples than Europeans and other New Zealanders in 2019. Like Māori, Pacific asthma patients were notably over-represented in New Zealand admissions for asthma in both 2010 and 2019 (Chan et al.2023).

Background

9.9. The Committee noted several treatments had been previously considered, including benralizumab, mepolizumab and omalizumab, which are funded for severe asthma. Full details on the consideration of these treatments can be found on the Application Tracker.

Health need

9.10. The Committee noted benralizumab and mepolizumab are funded for the first line biologic treatment of individuals with severe eosinophilic asthma (eosinophil count (EOS) >500 cells/µL), and omalizumab is funded for the first line biologic treatment of allergic immunoglobulin E (IgE) asthma. The Committee considered there were a number of people who were ineligible to receive the currently funded biologics. The Committee considered these individuals would receive high dose inhaled corticosteroids (ICS) and additional inhaled long-acting beta-agonist (LABA) or other maintenance medicine(s).

9.11. The Committee noted the Global Initiative for Asthma (GINA) 2020 global strategy for asthma management and prevention (2020) reported that 17% of people with asthma had poor symptom control despite being on GINA step 4 or 5 treatments. Of those on step 4 or 5, 3.7% were considered severely symptomatic and had poor symptom control despite good adherence and inhaler technique. The Committee considered that approximately 4.3% of people with asthma in New Zealand would be classified similarly.

9.12. The Committee noted the Chen et al. Curr Med Res Opin. 2018;34:2075-88 meta-analysis, which reported that between 3.2% and 10% of people with asthma (using the GINA step 4 or 5 treatments) would have severe uncontrolled asthma. The Committee noted individuals with severe uncontrolled asthma had on average an Asthma Control Test (ACT) score 7 points lower than those with moderate to severe controlled disease, and an Asthma Quality of Life Questionnaire score 1.3 lower comparatively. The

Committee noted the current Special Authority criteria for biologic treatment requires an ACT score of 10 or less, and the Committee considered that this threshold accurately identifies individuals with very severe disease.

9.13. The Committee noted Wang et al. Chest. 2020;157:790-804, which described the demographic and clinical characteristics of individuals treated in severe asthma services in the United States, Europe, and the Asia-Pacific region between 2014-2017. The Committee noted it included a web-based database that incorporated data from New Zealand. The study reported that overall, 25% of individuals were treated with biologic treatments. The Committee noted that 43.7% of people with uncontrolled asthma at GINA step 5 had low IgE concentrations (IgE< 150 iu/ml), and overall 26.2% of the cohort (including New Zealand data) had an eosinophil count (EOS) of >450 cells/µL. The Committee therefore considered approximately two thirds of people with ≥4 exacerbations a year would not currently fulfil the EOS Special Authority criteria to receive a biologic drug, and therefore have an unmet health need.

9.14. The Committee noted Shantakumar et al. Multidiscip Respir Med. 2020;15:662, which estimated that 28.8% of people with a phenotype of severe eosinophilic asthma had ≥4 annual exacerbations and would be eligible for treatment with a biologic in New Zealand. The Committee considered this estimate similar to that of the Wang et al. 2020 study.

Health benefit

9.15. The Committee noted Menzies-Gow et al. N Engl J Med. 2021;384:1800-9, which reported the results of the NAVIGATOR trial. This phase three, multicentre, randomised, double-blind trial included 1061 people with asthma controlled by ICS's and had experienced ≥2 exacerbations that led to systemic glucocorticoid use, emergency department visit or hospitalisation in the last 12 months.

9.15.1. The Committee noted the annualised rate of asthma exacerbations at week 52 were 0.93 (95% confidence interval [CI], 0.80 to 1.07) with tezepelumab treatment compared to 2.10 (95% CI, 1.84 to 2.39) with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001)

9.15.2. The Committee considered the greatest effect was in individuals with a high EOS at baseline (300 to ≤450, and ≥450 cells/µL), however effects were statistically significant across all EOS (<150 to ≥450 cells/µL).

9.15.3. The Committee noted the forced expiratory volume in 1 second (FEV_1) improved by 0.13 Liter (L) compared with placebo (0.23L vs. 0.09L; difference, 0.13L; 95% CI, 0.08 to 0.18; P<0.001). However, this did not meet the threshold for a minimally clinically important difference (MCID).

9.15.4. The Committee considered NAVIGATOR to be of high quality, and generalisable to the New Zealand population.

9.16. The Committee noted Corren et al. N Engl J Med. 2017;377:936-46, which reported the results of the PATHWAY trial. This phase two, multicentre, randomised, double-blind trial included 550 people with asthma not well controlled despite LABAs in combination with medium or high dose ICS, that had experienced ≥2 exacerbations that led to systemic glucocorticoid use, or ≥1 exacerbation that led to hospitalisation in the last 12 months. The Committee noted the trial considered three doses, and the 210 mg dose was selected for future phase three studies.

9.16.1. The Committee noted tezepelumab treatment resulted in annualised rates of asthma exacerbations at week 52 of 0.27, 0.20, and 0.23 in the low, medium, and high-dose groups, respectively, as compared with 0.72 in the placebo group. The exacerbation rates were lower in the tezepelumab groups than in the placebo group by 62% (90% confidence interval [CI], 42 to 75; P<0.001), 71% (90% CI, 54 to 82; P<0.001), and 66% (90% CI, 47 to 79; P<0.001), respectively. The Committee considered health benefit was observed irrespective of the baseline EOS, and of T-helper 2 (Th-2) biomarker status (a marker of allergic asthma).

9.17. The Committee noted Menzies-Gow et al. Lancet Respir Med. 2023;11:425-38, which reported the results of the DESTINATION study, an extension study that recruited individuals from the NAVIGATOR (n=824 people) and SOURCE (n=124 people) trials. The Committee considered the results suggested a continuing health benefit from tezepelumab over two years, with no waning of effect. The Committee noted there was an unexplained high rate of cardiac adverse events for tezepelumab compared with placebo (0.65 events per 100 patient years compared with 0.46 events). The Committee noted the most common adverse events were arthralgia and pharyngitis. The Committee considered overall the treatment appeared to be well tolerated.

9.18. The Committee noted Wechsler et al: Lancet Respir Med 2022;10: 650–60, which reported the results of the SOURCE trial. This phase three, multicentre, randomised, double-blind trial included 150 people who had received medium or high dose ICS and had ≥1 exacerbation in the past 12 months.

9.18.1. The Committee noted that the primary end point was different to the other two trials, with a percentage reduction from baseline in daily oral corticosteroid dose at week 48 without the loss of asthma control. The Committee noted the study reported similar results with tezepelumab vs placebo in the overall population (odds ratio [OR] 1·28 [95% CI 0·69-2·35], P=0·43; primary endpoint not met). The percentage change was higher with tezepelumab vs placebo in participants with baseline blood EOS of ≥150 cells/µL (2·58 [1·16-5·75]), but not in participants with counts below 150 cells/µL (0·40 [0·14-1·13]).

9.19. The Committee noted Biener et al. J Allergy Clin Immunol Pract. 2024; 12: 2399-407.e5, a retrospective multicentre longitudinal follow-up study that included individuals who had switched from other biologics. The study reported the health benefit in individuals who had switched treatment were smaller than individuals who had not received prior biologic therapy. The Committee noted high rates of discontinuation (18.2%), that were considered largely due to lack of efficacy.

9.20. The Committee considered overall that treatment with tezepelumab reduced exacerbations and hospitalisations. The Committee noted oral corticosteroid usage was not reduced in the SOURCE study, but considered it was reasonable that oral corticosteroid use may lessen due to a reduced exacerbation rate.

9.21. The Committee noted Bleecker et al. Lancet. 2016;388:2115-27 and FitzGerald et al. Lancet. 2016;388:2128-41, which reported the results of benralizumab in similar trial populations. The Committee considered it reasonable to consider tezepelumab as non-inferior to benralizumab in individuals with eosinophilic asthma eligible for current biologic treatment.

9.22. The Committee noted Humbert et al. Allergy. 2005;60:309-16, which reported the results of omalizumab in the treatment of allergic asthma (INNOVATE trial). The Committee considered it was difficult to compare between the trials as there was no stratification in the tezepelumab trials according to IgE levels. The Committee noted that the mean IgE levels were higher in the NAVIGATOR study compared to the INNOVATE study. The Committee considered it was reasonable to consider tezepelumab as non-inferior to omalizumab in individuals with allergic asthma eligible for current biologic treatment.

Suitability

9.23. The Committee noted tezepelumab can be self-administered as a subcutaneous injection, at the same frequency as omalizumab and mepolizumab. The Committee noted tezepelumab would require more frequent administration compared with benralizumab.

Cost and savings

9.24. The Committee considered that, based on the Shantakumar et al. Multidiscip Resp Med. 2020;15:662 study, approximately 4.3% of individuals would have uncontrolled eosinophilic asthma with ≥4 annual exacerbations. The Committee considered that approximately 26.4% of the New Zealand population with asthma have undergone

phenotyping. Therefore, the Committee considered in New Zealand approximately 5,676 people would have severe uncontrolled eosinophilic asthma with ≥4 annual exacerbations. The Committee noted that an estimated 53.9% of individuals would adhere to ICS/LABA therapy (Perrin et al. J Allergy Clin Immunol. 2010;126:505-10), and therefore considered approximately 3000 people would be eligible for treatment with current biologic therapy.

9.25. The Committee considered approximately 1000 people with eosinophilic asthma in New Zealand would have EOS >500 cells/µL, whilst 2000 people would have counts <500 cells/µL. The Committee considered that the number of people with EOS >500 cells/µL may be underestimated by cross sectional studies due to variations in eosinophil numbers over time. The Committee considered there was a lack of data on EOS for individuals with allergic phenotype asthma, however considered most individuals would have a high EOS.

9.26. The Committee noted Reibman et al. Ann Allergy Asthma Immunol. 2021;127:318-25, which reported 29% of 3,262 patients receiving a biologic for asthma in a retrospective US database study had severe uncontrolled asthma despite treatment with biologics. The Committee noted that the majority of people (88%) received omalizumab, which is less frequently used in New Zealand. The Committee considered that although 63% of people enrolled in the study had at least one annual exacerbation, it is likely that control in these individuals would be significantly better than in individuals who would be eligible to initiate biologic treatment in New Zealand (≥4 annual exacerbations at baseline). Therefore, the Committee considered it is not necessarily as likely that 29% of those receiving biologics for asthma in New Zealand would wish to switch between treatments, but there was no clear evidence to suggest these figures would not apply to New Zealand.

9.27. The Committee considered it was reasonable to assume a 56% reduction in annual exacerbations, based on the NAVIGATOR study in individuals with severe uncontrolled asthma.

9.28. The Committee considered it was reasonable to assume a 77% reduction in annual exacerbations, based on the NAVIGATOR study in individuals with eosinophilic asthma, based on the subgroup with an EOS of ≥450 cells/µL.

9.29. The Committee considered there was a lack of data for individuals with allergic IgE asthma, but noted the treatment exacerbation rate in the NAVIGATOR trial was independent of IgE level.

9.30. The Committee considered it was reasonable to assume a 51% reduction in annual exacerbations, based on the NAVIGATOR study in individuals with non-allergic asthma, a reduction of 39% in individuals with non-eosinophilic asthma with EOS<150 cells/µL, a 41% reduction in individuals with an EOS<300 cells/µL, and a 46% reduction if EOS <450 cells/µL.

9.31. The Committee considered it was reasonable to assume a reduction in the rate of exacerbations associated with hospitalisation or an emergency department visit, based on the reported rate ratio of 0.21 (95% CI, 0.12 to 0.37) from the NAVIGATOR study.

9.32. The Committee recommended the Respiratory Advisory Committee provide an estimate of the length of time on treatment for tezepelumab.

9.33. The Committee considered there was no evidence of treatment waning after 104 weeks, based on the DESTINATION trial. The Committee considered there was a high discontinuation rate, based on Reibman et al. 2021, but noted that the majority of people discontinuing in that trial had switched from another biologic treatment.

9.34. The Committee considered that approximately twice as many people would become eligible for tezepelumab, compared to those currently accessing treatment for currently funded biologic agents, due to these individuals not currently meeting the EOS criteria. The Committee considered that the estimated uptake of 10% seemed low, with approximately 75% of eligible individuals with an EOS >500 cells/µL currently receiving biologic treatment.

9.35. The Committee considered uptake of tezepelumab would initially be 10% in the first- line biologic setting for those eligible for the existing biologics due to clinician familiarity,

increasing to the same percentage as benralizumab over time. The Committee considered that all individuals with an EOS <500 cells/µL would initiate treatment with tezepelumab as they would not be eligible for treatment with other first -line biologics.

9.36. The Committee noted Pharmac staff had clarified that the intent of the supplier application was for tezepelumab to be used as a first-line biologic. However, the Committee considered that some individuals who are currently receiving first-line biologic treatments may wish to switch to tezepelumab if funded in subsequent lines, as, despite fulfilling renewal criteria, their asthma may not be well controlled on their current treatment. The Committee considered there was insufficient evidence on the switching of treatment from currently funded biologics to tezepelumab or vice versa. The Committee considered this lack was due to tezepelumab's recent introduction to the market. The Committee considered it reasonable to assume efficacy would be similar to other within-indication switches. The Committee again noted the Biener et al. 2024: study, which reported lower efficacy in individuals who switched from prior biologics, but noted this study was small (n=129 participants).

Funding criteria

9.37. The Committee considered it was not appropriate for tezepelumab to be used in combination with any other funded biologics for the treatment of asthma. The Committee considered all currently funded biologics for severe asthma should not be used in combination with other first-line biologics and the Special Authority for omalizumab should be amended to reflect this.

Summary for assessment

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

Population	People with severe uncontrolled asthma, defined as either: • Experiencing ≥4 exacerbations per year needing systemic corticosteroids, OR • Requiring maintenance oral corticosteroids (OCS), despite the use of high-dose inhaled corticosteroids (ICS) and additional inhaled long-acting beta-agonist (LABA) or other maintenance medicine. Therefore, the population would include the following groups (first-line biologic use): • Groups 1-3: People who would be eligible to commence treatment with currently funded biologics (i.e. mepolizumab or benralizumab for those with severe eosinophilic asthma; or omalizumab for those with severe allergic asthma), and • Group 4: People who are ineligible for currently funded biologics because they have non-allergic or non-eosinophilic asthma phenotypes.	
Intervention	First-line biologic treatment with subcutaneous tezepelumab 210 mg every 4 weeks. Treatment is assumed to be ongoing for as long as the patient continues to experience adequate asthma control, until renewal criteria are not met.	
Comparator(s)	Four comparators (aligning with groups 1-4) in the first-line biologic setting: • Severe eosinophilic asthma (EOS >500): 1. Subcutaneous benralizumab 30 mg every 4 weeks for 3 doses, followed by a maintenance dose every 8 weeks. 2. Subcutaneous mepolizumab 100 mg every 4 weeks • Allergic IgE asthma: 3. Subcutaneous omalizumab, dose and frequency is determined by baseline immunoglobulin E and body weight (See Medicine Data Sheet) • Ineligible for currently funded biologics: 4. High dose ICS and LABA or other maintenance medicine +/- OCS as per 2020 Adolescent and Adult Asthma guidelines.	
Outcome(s)	Groups 1-3 – Non-inferior asthma control in terms of exacerbations and exacerbations leading to ED visits or hospitalisations.	Group 4 • NAVIGATOR reported a reduction in exacerbations compared to placebo (RR, 0.44; 95% CI, 0.37 to 0.53; P<0.001). • NAVIGATOR reported reductions in exacerbations leading to ED visits or hospitalisations (RR, 0.21; 95% CI, 0.12 to 0.37).
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. Testosterone cream - For the treatment of hypoactive sexual desire dysfunction (HSDD) in postmenopausal women

Application

10.1. The Committee reviewed the supplier application from Alchemy Health Limited for testosterone 1% w/v cream (AndroFeme 1) for the treatment of hypoactive sexual desire dysfunction (HSDD) in post-menopausal women.

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

Recommendation

10.3. The Committee **recommended** that testosterone 1% w/v cream (AndroFeme 1) for the treatment of hypoactive sexual desire dysfunction in post-menopausal women be **declined**.

10.4. In making this recommendation, the Committee considered:

10.4.1. the uncertain diagnostic requirements for HSDD in post-menopausal women, potentially leading to inappropriate diagnosis and treatment, and noting a lack of clear clinical guidelines relevant to the New Zealand context

10.4.2. the eligibility criteria proposed as part of the application for AndroFeme 1 were not appropriate and posed significant barriers to equitable access for women, especially for some cultures who would not wish to undergo aspects of an HSDD diagnosis

10.4.3. the uncertain health benefit of AndroFeme 1 compared with funded testosterone gel (Testogel) [unapproved / off-label use]

10.4.4. the potential suitability issues in administering appropriate doses of Testogel for women, and a lack of data around the impact of this given the currently increasing use of Testogel by women

10.4.5. that the use of Testogel at equivalent mg dosages to AndroFeme 1 does not create a risk of supraphysiological levels of testosterone, given that the available pharmacokinetic data could not reasonably be generalised to suggest significant bioavailability differences between Testogel and AndroFeme 1 at equivalent milligram dosages

10.4.6. that there was poor understanding of long-term side effects due to a lack of evidence of the long-term use of testosterone in women. The Committee considered that potential virilising side effects from short term testosterone use can often be managed through appropriate treatment monitoring and adjustment.

10.5. The Committee considered that Pharmac could seek further clinical advice from the Reproductive and Sexual Health Advisory Committee and/or Endocrinology Advisory Committee regarding their views on the application and this discussion, and if there were subgroups of post-menopausal women with HSDD who might have a higher unmet need.

Discussion

Māori impact

10.6. The Committee discussed the impact of funding testosterone 1% w/v cream (AndroFeme 1) for the treatment of HSDD on Māori health areas of focus and Māori health outcomes. The Committee considered it was not aware of studies reporting the prevalence or health outcomes of HSDD among Māori. HSDD is not one of Pharmac's Hauora Arotahi | Māori Health Areas of Focus. The Committee considered there may be barriers to diagnosis of HSDD and subsequent treatment.

Populations with high health needs

10.7. The Committee discussed the health needs of people with HSDD among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding testosterone 1% w/v cream (AndroFeme 1) and considered it was not aware of studies reporting the prevalence or health outcomes of HSDD among populations with high health needs.

Background

10.8. The Committee noted that from 1 April 2024, testosterone transdermal gel 16.2 mg/g (Testogel) was listed on the Pharmaceutical Schedule without restriction. This decision was the result of a Request for Proposals (RFP) by Pharmac for the supply of non-injectable testosterone. The Committee noted that it had previously reviewed a funding application for testosterone gel in May 2022 following a supply issue with testosterone undecanoate capsules and provided advice ahead of an RFP planned by Pharmac for non-injectable testosterone. At that time, the Committee had recommended that a testosterone gel product be funded with a high priority for testosterone replacement therapy.

Health need

10.9. The Committee noted the application describes hypoactive sexual desire dysfunction (HSDD) as being characterised by the persistent or recurrent absence of sexual fantasies and thoughts, and/or desire for or receptivity to sexual activity. The application indicates that the condition is of a degree that results in personal distress and/or difficulties in inter-personal relationships. The Committee considered that sexual difficulties may be lifelong, acquired, situational or generalised. The Committee considered that HSDD is often multifactorial and biopsychosocial factors may play causative and/or contributory roles in its development, which adds complexity to the process of reaching a diagnosis.

10.10. Members considered that HSDD can occur as part of menopause, but it can also occur at other life stages and for a range of reasons such as due to previous trauma, medication, pregnancy or recent childbirth, stress, and relationship issues. The Committee noted that the group targeted by the funding application for AndroFeme 1 was post-menopausal women. The Committee noted that the average age range for menopause in New Zealand is 45 to 55 years and that about 70% of women will have significant menopause symptoms (Healthify, 2024). Members noted that about 40% of women are reported to see a doctor because of their menopause symptoms. The Committee noted that there has been a significant increase in demand for menopause-related care and oestradiol based hormonal replacement (MHT) therapy in recent years.

10.11. The Committee noted that some women with HSDD have reported impaired body image, self-confidence, self-worth and disconnection to their intimate partners (Goldstein et al. Mayo Clin Proc. 2017;92:114-28). The Committee noted that the impact of HSDD can extend to the sexual partners' intimate relationships, with some partners reporting that HSDD has a negative impact on them and decreased their relationship strength (Simon et al. J Womens Health (Larchmt). 2022; 31: 715–-25). The Committee noted that the submission included comments from partners of women with HSDD which considered that treatment of HSDD would help alleviate the burden felt by partners of individuals with HSDD. Members considered that this would likely be an improvement in quality of life, acknowledging that this was based on reports of lived experience rather than quantitative evidence published in the medical literature.

10.12. The Committee considered the approach to reaching a diagnosis of HSDD in a woman with clinically significant personal distress from HSDD is complex and multi-factorial. The Committee noted reaching a diagnosis for HSDD requires a comprehensive patient history, pelvic examination, blood tests, questionnaires, and a screening assessment for decreased sexual desire. The Committee noted there were a range of questionaries available to support assessment and considered the questionnaires used were varied and most were validated in small scale studies. The Committee considered that some women would not be comfortable to initiate or undergo the comprehensive diagnostic assessment for HSDD proposed for access as part of the supplier application and that, as a result, some women may receive a provisional diagnosis rather than undergo the full testing. The Committee therefore considered that there was a risk of inaccurate diagnosis of HSDD and many women may be underdiagnosed, or wrongly diagnosed, or receive pharmacological treatment earlier in the treatment paradigm than appropriate.

10.13. The Committee considered that it was uncertain which questionnaire would be most relevant to the New Zealand setting, and that additional education and training through the Health Pathways forum would be valuable for standardising diagnosis and treatment.

10.14. The Committee noted the following studies regarding the prevalence of HSDD among postmenopausal women and testosterone usage:

- Leiblum et al. Menopause. 2006 ;13:46-56
- Dennerstein et al. J Sex Med. 2006;3:212-22
- West et al. Arch Intern Med. 2008;168:1441-9
- Worsley et al. J Sex Med. 2017; 14:675-86

- Zeleke et al. Menopause. 2017;24:391-9
- Agrawal et al. J Sex Med. 2024;21:288-93

10.15. The Committee noted that the scales or questionnaires used to assess HSDD in these prevalence studies varied and that the diagnostic process was less rigorous in some studies. The Committee noted that the data suggested prevalence was 16% to 26% in young women who experienced surgical menopause, 6.6% to 9% in those who experienced natural menopause, and slightly less for older women who had experienced surgical menopause. However, the Committee considered these estimates were highly uncertain given the issues regarding scales, questionnaires, and diagnosis in the studies, the high proportion of women experiencing significant menopause symptoms, and the low (but possibly increasing) proportion who would see a doctor because of their symptoms.

10.16. The Committee noted a New Zealand based survey, with responses from over 4000 people. The survey identified that menopause had a negative effect on the sex life of 85% of respondents, 88% on their relationship with their partner, and 57% on their relationship with their children (Menodoctor Survey Report, 2023).

10.17. The Committee considered that current treatment options for HSDD for post-menopausal women include funded off-label use of Testogel, privately funded AndroFeme 1 or compounded testosterone cream, sexual therapy (which is available privately) in addition to treatment of genitourinary symptoms of menopause, oestrogen replacement and treatment of co-morbid mental health conditions such as anxiety and/or depression. In addition, relationship counselling, and cognitive behavioural therapy or other psychological interventions can be used.

10.18. The Committee noted the 2019 Global Consensus Position Statement on the Use of Testosterone Therapy for Women, which had been endorsed by The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). The statement recommended testosterone therapy for post-menopausal women with HSDD in doses that approximate physiological testosterone concentrations for pre-menopausal women, and off-label prescribing of an approved male formulation provided hormone concentrations are maintained in the physiologic female range. The Committee also noted that in response to a consultation to fund Testogel, the RANZCOG:

10.18.1. indicated that women with HSDD would benefit from a testosterone product being available, but that a lower strength product would be easier to administer

10.18.2. requested that funded indications of testosterone be expanded to include HSDD in post-menopausal women.

10.19. The Committee noted that since the funding of Testogel in February 2024, there have been 2,300 people dispensed Testogel and approximately 46% of these people identify as the female gender. The Committee noted that a large proportion of women dispensed Testogel were in the age range of 40 to 60 years, highlighting likely off-label use of Testogel for HSDD in menopause. The Committee noted testosterone usage in the UK, which demonstrated stable use of testosterone over time in males, but rising use of all testosterone products since 2021. The Committee considered this increase was likely associated with the growing awareness and benefits of hormonal treatments (MHT) in menopause.

10.20. The Committee noted one pump of Testogel delivers 20.25 mg of testosterone in 1.25 g of gel, and if this quantity was applied it would deliver a higher dose than is required for the treatment of HSDD in women. However, there is uncertainty because absorption through the skin is poor, with associated low plasma concentration and considerable variability. The Committee noted the recommended off-label dose of Testogel (20.25 mg / 1.25 g) outlined by the British Menopause Society is 5 mg or equivalent to one quarter of one pump actuation from the current bottle. The Committee noted safe prescribing would require prescribers to educate users on the total volume of gel that should be used. The Committee noted anecdotal reports of Testogel use in New Zealand, where administering a one quarter pump dose of Testogel is challenging but possible by dispensing one pump

actuation of the product into a small container and using an insulin syringe to aliquot an appropriate dose. The Committee noted there are also actuation devices available for purchase privately that can dispense an amount of Testogel equivalent to a 5mg dose.

10.21. The Committee considered that adverse effects related to the administration of testosterone in women included acne and oily skin, increased body hair particularly on the face, thinning or loss of head hair (male pattern baldness), headache, abdominal bloating, constipation, symptoms of an allergic reaction, nausea and vomiting, yellowing of the skin and/or eyes, swelling of the ankles, weight gain, persistent headaches, deepening of the voice, changes in tissue of the breast, vaginal bleeding, ovulation and menstrual periods stopping in pre-menopausal women, and enlargement of the clitoris. The Committee also noted the lack of long-term safety data for cardiovascular and breast outcomes.

10.22. The Committee considered the adverse effects related to the administration of testosterone are an important consideration when initiating testosterone treatment in women, but most can be reasonably mitigated with appropriate monitoring of treatment.

Health benefit

10.23. The Committee noted El-Hage et al. Climacteric. 2007;10:335-43, a double-blind, randomised, cross-over study of post-menopausal women (n=36) who received cutaneous 10 mg AndroFeme 1 or placebo for 12 weeks.

10.23.1. The primary outcome was assessed by a sexuality score from the Brief Index of Sexual Function for Women (BISF-W), which measures sexual desire, arousal, frequency of sex, receptivity/initiation, pleasure/orgasm, relationship satisfaction and sexual problems.

10.23.2. At 12 weeks, BISF-W sexuality score increased from a baseline score of 19.85 by a mean 8.76 (± SD 7.46) in the testosterone group and from a baseline score of 21.05 by 0.54 (± 9.16) in the placebo group (difference in change in score after treatment p<0.000). No safety concerns were reported in the paper.

10.23.3. The Committee noted the study was small, with 36 people included. The population was heterogeneous, including those who had undergone hysterectomy (with or without removal of one or both ovaries) and excluded women receiving antidepressants. The Committee noted that individuals were recruited to the study through newspaper and internet advertisements. The Committee noted that there was a lack of clarity on some of the eligibility criteria, for example that the person must be in a stable relationship of at least six months as assessed by the sex therapist, but there were no further details provided as to what 'stable' was.

10.23.4. The Committee noted the BISF-W is a 91-point scale (-16 indicating poor function and +75 indicating maximal function) and that a minimally clinically important difference has not been established for this survey. The Committee considered it was difficult to determine the clinical significance of the 8.8 point increase from baseline considering the score covers seven different domains and the treatment duration was a short period of 12 weeks.

10.24. The Committee noted Islam et al. Lancet Diabetes Endocrinol. 2019;7:754-766 the systematic review and meta-analysis regarding safety and efficacy of testosterone via oral, patch, implant and topical administration routes. Women of pre/post-menopausal status were included in the publication. The analysis included 36 studies with 8000 participants.

10.24.1. The authors reported that, compared with placebo or a comparator (oestrogen, with or without progestogen), testosterone improved sexual function, including the number of satisfactory sexual events per month (mean difference 0·85, 95% CI 0·52 to 1·18) and increased sexual desire scores (standardised mean difference 0·36, 95% CI 0·22 to 0·50) in post-menopausal women.

10.24.2. The Committee noted that the authors also reported pooled results for improvements in pleasure, arousal, orgasm, responsiveness, self-image, reduced sexual concerns, and distress in post-menopausal women.

10.24.3. The Committee considered that the results of this analysis indicated an improvement in sexual outcomes from testosterone treatment, but the outcomes reported in the study were not validated as to their clinical significance.

10.24.4. Additionally, the Committee considered that this evidence was unable to confirm how the health benefits of testosterone cream (AndroFeme 1) might compare with those from funded testosterone gel (Testogel) due to the small number of studies for each of these formulations, each for different populations and clinical indications.

10.24.5. The Committee noted oral administration of testosterone resulted in significantly increased low-density lipoprotein (LDL)-cholesterol, with reductions in the amounts of total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides. In addition, regardless of administration route, testosterone administration increased peoples' weight and was associated with a significantly greater likelihood of reporting new acne and hair growth.

10.25. The Committee noted the applicant had provided Wittert et al. Andrology. 2016;4:41-5; an open-label, phase 2, randomised crossover pharmacokinetic study comparing testosterone gel 1% (50 mg dose) and Androforte 5% testosterone cream (100 mg dose). The Committee noted the study was conducted in 16 Caucasian males aged 29 to 73 years, with male hypogonadism and an average BMI of 30.7 kg/m^2.

10.25.1. The Committee noted the authors reported bioequivalence between the two products at different dosages, but considered the study design and report to be of average quality and indicated wide ranges for pharmacokinetic outputs, highlighting variability in testosterone absorption between individuals who administer testosterone at a set dose.

10.25.2. Members further noted greater variation in measured blood testosterone level with the lower concentration formulation, although the lack of sample size estimates and potential contribution of endogenous testosterone meant the generalisability of this finding was unclear.

10.25.3. The Committee noted that the applicant had considered that the results of this pharmacokinetic study supported a claim that Testogel was twice as potent as AndroFeme 1, but the Committee considered it was unreasonable to generalise the results of Wittert et al. 2016 to suggest significant bioavailability differences between Testogel and AndroFeme 1 at equivalent dosages.

10.26. Overall, the Committee considered the evidence for use of testosterone for the treatment of HSDD was of poor quality and low strength, and that the evidence for testosterone cream (AndroFeme 1) in HSDD came from one underpowered study. The Committee considered the evidence indicated improved sexual outcomes from testosterone treatment compared to placebo with or without oestradiol-based HRT, but outcomes were limited by the lack of validation of clinical significance. The Committee acknowledged that menopause specialists and RANZCOG supported and endorsed the use of testosterone in post-menopausal women based on the available evidence. The Committee considered that the available evidence likely has limited generalisability to the New Zealand context given there were no New Zealand individuals included in the studies and New Zealand is likely to have different cultural constructs, experiences and views toward menopause treatment as well as differing levels of awareness and access to MHT and other treatments in our health care system.

10.27. The Committee noted there are many people currently receiving Testogel, and considered it would be difficult to quantify any significant differences in health outcomes if the post-menopausal women among them were to switch to AndroFeme 1. However, the Committee acknowledged that many individuals would prefer AndroFeme 1 due to it being easier to self-administer in smaller doses than Testogel.

10.28. The Committee considered there was a lack of published evidence of any partner benefits from testosterone treatment for HSDD, although it was likely that any clinically significant improvement in HSDD experienced by the individual would result in benefit for partners.

10.29. The Committee noted the available evidence reported no significant safety concerns from the use of testosterone in HSDD, but there is a lack of long-term safety data on the use of testosterone in this population.

Suitability

10.30. Members considered that testosterone absorption through the skin is poor, with topical formulations being associated with low plasma concentration and considerable variability in absorption.

10.31. The Committee considered that AndroFeme 1 has clear suitability advantages compared to Testogel with administering a recommended dose of 5 mg to 10 mg. The Committee noted that AndroFeme 1 contains a dose applicator with 0.25 ml graduations to enable titrating dosages by 2.5 mg, whereas Testogel delivers one pump actuation equivalent to 20.25 mg testosterone, which would require quartering or halving to achieve an appropriate dose. The Committee considered that if a woman-specific product were funded, prescribing GPs, nurse practitioners (NPs) and other primary care prescribers including pharmacist prescribers would be more comfortable prescribing testosterone cream compared with Testogel.

Cost and savings

10.32. The Committee considered the number of postmenopausal women requiring testosterone treatment for HSDD is unclear, but there may be an increase in GP appointments to discuss treatment if this cream was funded. The Committee considered that the assessment and diagnosis of HSDD is likely to occur in primary care. The Committee considered access to specialist services to support assessment and diagnosis would be limited considering a lack of additional capacity in these services currently.

10.33. The Committee considered that the number of people accessing Testogel for post-menopausal HSDD will continue to grow. The Committee also considered that funding of AndroFeme 1 would likely increase the overall number of people treated.

10.34. The Committee considered the likely proportion of post-menopausal women with HSDD who would require testosterone treatment following insufficient health benefit from addressing biopsychological factors was uncertain. The Committee considered that treatment approaches for addressing biopsychosocial factors would be difficult to access for many people and that testosterone treatment may be pursued instead of these approaches.

10.35. The Committee considered it was uncertain of the overall rate of HSDD in post-menopausal women in New Zealand, given the variation in prevalence data available and limitation in various questionnaires used in available epidemiological studies. The Committee considered that results from the New Zealand-based Menodoctor survey (Menodoctor Survey Report, 2023) suggested there could be significantly high rates of post-menopausal women seeking treatment for HSDD and considered it would be reasonable for Pharmac staff to use this to help inform group size estimates.

General

10.36. The Committee noted that the access criteria for AndroFeme 1 proposed by the applicant would require a patient to:

- be aged 18 years or older
- have a confirmed and documented diagnosis of HSDD
- be considered naturally or surgically post-menopausal

- have received insufficient benefit from education and correction of modifiable biopsychosocial factors according to the International Society for the Study of Women's Sexual Health.

10.37. The Committee considered there would be significant variation in access to appropriate assessment and diagnosis of HSDD and in treatments required to address modifiable biopsychosocial factors. The Committee considered that access would likely be inequitable under the access criteria proposed, which were more stringent than the open-listed current funded product and posed significant access barriers for women, especially for some cultures who would not wish to undergo aspects of a comprehensive diagnostic assessment. The Committee considered the requirement for a pelvic exam could be a barrier to access.

10.38. The Committee considered funding AndroFeme 1 without any schedule restriction would support equitable access, but considered there would be a risk of over-prescribing. The Committee considered there is a concern that due to the increased visibility of products through advertisement and social media there may be an increase in prescribing or administration to individuals without an appropriate assessment and diagnosis of HSDD. The Committee considered that strong marketing of a testosterone product approved for female use would increase the risk of inappropriate prescribing and use in individuals with less capacity to benefit. The Committee considered that appropriate prescribing of testosterone for HSDD could be supported by a Health Pathways update for primary care.

10.39. The Committee recommended Pharmac staff seek advice from the Reproductive and Sexual Health Advisory Committee and/or the Endocrinology Advisory Committee to ascertain if there were subgroups of post-menopausal women with HSDD who might have a higher unmet need (for example if unable to trial oestradiol-based hormone replacement therapy for HSDD, or it would be inappropriate to do so).

11. Ocrelizumab subcutaneous formulation – multiple sclerosis (same as IV funded indications)

Application

11.1. The Committee reviewed the application for subcutaneous (SC) ocrelizumab for the treatment of the same indications as the intravenous (IV) formulation (relapsing remitting multiple sclerosis, and primary progressive multiple sclerosis).

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

Recommendation

11.3. The Committee **recommended** that subcutaneous ocrelizumab for the treatment of the same indications as the intravenous formulation (relapsing remitting multiple sclerosis, and primary progressive multiple sclerosis) be listed with a **high priority** subject to the same Special Authority criteria as the IV formulation, ie:

Relapsing remitting multiple sclerosis

Initial application — (Multiple Sclerosis – ocrelizumab) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
Either:
1. All of the following:
   - 1.1 Diagnosis of multiple sclerosis (MS) meets the McDonald 2017 diagnostic criteria for MS and has been confirmed by a neurologist; and
   - 1.2 Patients has an EDSS score between 0 – 6.0; and
   - 1.3 Patient has had at least one significant attack of MS in the previous 12 months or two significant attacks in the past 24 months; and
   - 1.4 All of the following:
     - 1.4.1 Each significant attack must be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the attack, but the neurologist/physician must be satisfied that the clinical features were characteristic); and

1.4.2 Each significant attack is associated with characteristic new symptom(s)/sign(s) or substantially worsening of previously experienced symptoms(s)/sign(s); and
1.4.3 Each significant attack has lasted at least one week and has started at least one month after the onset of a previous attack (where relevant); and
1.4.4 Each significant attack can be distinguished from the effects of general fatigue; and is not associated with a fever (T> 37.5°C); and
1.4.5 Either:
1.4.5.1 Each significant attack is severe enough to change either the EDSS or at least one of the Kurtze Functional System scores by at least 1 point; or
1.4.5.2 Each significant attack is a recurrent paroxysmal symptom of multiple sclerosis (tonic seizures/spasms, trigeminal neuralgia, Lhermitte's symptom); and
1.5 Evidence of new inflammatory activity on an MRI scan within the past 24 months; and
1.6 Any of the following:
1.6.1 A sign of that new inflammatory activity on MRI scanning (in criterion 5 immediately above) is a gadolinium enhancing lesion; or
1.6.2 A sign of that new inflammatory activity is a lesion showing diffusion restriction; or
1.6.3 A sign of that new inflammatory is a T2 lesion with associated local swelling; or
1.6.4 A sign of that new inflammatory activity is a prominent T2 lesion that clearly is responsible for the clinical features of a recent attack that occurred within the last 2 years; or
1.6.5 A sign of that new inflammatory activity is new T2 lesions compared with a previous MRI scan; or

2. Patient has an active Special Authority approval for either dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1-alpha, interferon beta-1-beta, natalizumab or teriflunomide.

Note: Treatment on two or more funded multiple sclerosis treatments simultaneously is not permitted.

Renewal — (Multiple Sclerosis - ocrelizumab) from any relevant practitioner. Approvals valid for 12 months where patient has had an EDSS score of 0 to 6.0 (inclusive) with or without the use of unilateral or bilateral aids at any time in the last six months (ie the patient has walked 100 metres or more with or without aids in the last six months).
Note: Treatment on two or more funded multiple sclerosis treatments simultaneously is not permitted.

Primary progressive multiple sclerosis

Initial application — (Primary Progressive Multiple Sclerosis) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Diagnosis of primary progressive multiple sclerosis (PPMS) meets the 2017 McDonald criteria and has been confirmed by a neurologist; and
2. Patient has an EDSS 2.0 (score less than or equal to 2 on pyramidal functions) to EDSS 6.5; and
3. Patient has no history of relapsing remitting multiple sclerosis.

Renewal – (Primary Progressive Multiple Sclerosis) from any relevant practitioner. Approvals valid for 12 months for applications where the patient has had an EDSS score of 2.0 to 6.5 (inclusive) at any time in the last six months (ie patient has walked 20 metres with bilateral assistance/aids, without rest in the last six months).
Note: Treatment on two or more funded multiple sclerosis treatments simultaneously is not permitted.

11.4. In making this recommendation the Committee considered:

11.4.1. the high demands on infusions services nationally

11.4.2. the non-inferior health benefit of the SC formulation compared with the IV formulation of ocrelizumab

11.4.3. the increased suitability benefit of the SC formulation for individuals, with reduced travel to infusion services and a reduced time for administration.

Discussion

Māori impact

11.5. The Committee discussed the impact of funding SC ocrelizumab for the treatment of relapsing remitting multiple sclerosis (RRMS), and primary progressive multiple sclerosis (PPMS) on Māori health areas of focus and Māori health outcomes. The Committee noted that multiple sclerosis (MS) is not one of the Hauora Arotahi | Māori health areas of focus, and that the prevalence of MS in Māori has been reported to be appreciably lower than in

non-Māori (Pearson et al. Mult Scler. 2014;20:1892-5; Pearson et al. Mult Scler. 2014;20:1892-5; Health NZ | Te Whatu Ora, 2024).

11.6. The Committee previously considered in August 2022 that the impact of MS, when it occurs, is likely to be greater in Māori, noting the higher representation of Māori in lower socioeconomic groups and the effect of this on functional needs and access to care and diagnostic support services. Pharmac staff consider that challenges in accessing specialist care would also be a contributing factor to the impact of MS on Māori when it occurs; this may be a direct difficulty accessing or attending specialist centres (for example due to travel cost or logistics, paid or community work commitments or childcare/family/whānau requirements) or indirectly arising from barriers to referral from primary care, such as the ability to attend a GP clinic or the cost of a GP visit.

Populations with high health needs

11.7. The Committee discussed the health needs of people with MS among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of funding ocrelizumab and considered:

11.7.1. that although the data is limited, Pacific peoples are less likely to be affected by MS given that evidence to date suggests that the disease predominantly affects those of Northern European ancestry (Taylor et al. Mult Scler. 2010;16:1422-31).

11.7.2. that access to neurology specialists in the public health system may currently be limited due to high demand, and it may be even more difficult for people living at a distance from secondary care i.e. those living in rural locations.

Background

11.8. The Committee reviewed an application for the SC formulation of ocrelizumab. The Committee noted the IV formulation is funded for both PPMS and RRMS.

Health need

11.9. The Committee noted the health need of individuals with either PPMS or RRMS was reviewed previously when considering treatment for MS.

11.9.1. The Committee noted a range of treatments are funded for MS. The Committee noted the orally administered treatments include dimethyl fumarate, fingolimod and teriflunomide. Natalizumab and ocrelizumab are funded IV treatments, whilst glatiramer acetate and interferon beta-1-beta are administered SC. Interferon beta-1-alpha is administered through intramuscular injection.

11.10. The Committee noted the supplier provided a New Zealand based survey of clinicians that focused on access to infusion services. The Committee noted the survey reported there were delays in access to first treatment, as well as regional variability in access. The survey reported that infusion services were becoming more difficult to access, however the Committee considered that the influence of this on health outcomes was uncertain.

Health benefit

11.11. The Committee noted the supplier provided a manuscript for the OCARINA I study that had been accepted for publication by the Annals of Clinical and Translational Neurology journal. This has since been published as Lawrence et al. J Neurol Neurosurg Psychiatry. 2024;95;A13-14. The dose escalation study was performed in 118 people with either RRMS or PPMS, previously treated with IV ocrelizumab or treatment naïve to ocrelizumab. The study reported that a dose of 920mg was optimal and provided a similar area under the time-concentration curve, as 600 mg IV ocrelizumab. The Committee considered the SC formulation was well tolerated across all dose levels tested in the dose escalation phase and the safety profile was similar to the IV formulation.

11.12. The Committee noted the supplier provided a manuscript for the OCARINA II study that is currently under peer review. The Committee noted the ongoing phase 3, non-inferiority, randomised, open-label, parallel-group, multicentre study was performed in 236 people with either RRMS or PPMS. The Committee noted that CD-19+ B cell counts were used as a surrogate marker of efficacy. The Committee considered that the SC formulation provided non-inferior efficacy compared to the IV formulation. The Committee noted that whilst most individuals did experience an adverse event, the majority (96.6%) were grade one or two in nature. The Committee considered that the safety profile of the SC formulation would not preclude its administration either in a GP surgery, or by a nurse, in a healthcare or home setting.

11.13. The Committee considered overall the trial evidence from the OCARINA I trial was of high quality. The Committee considered overall the data supported that the SC formulation provided non-inferior health benefit to the IV formulation of ocrelizumab. The Committee considered the results of the trial were generalisable to the New Zealand population.

11.14. The Committee noted a supplier performed patient reported outcomes survey that reported a high level of satisfaction for convenience and time taken for total treatment with the SC formulation.

Suitability

11.15. The Committee noted the six-monthly administration of the SC injection would significantly reduce the overall administration time in comparison to the IV formulation. The Committee noted direct administration time of the treatment was reduced from between 2 to 3.5 hours to 10 minutes. In addition, the time for pre-medication and observation post-administration would be reduced with the SC injection.

11.16. The Committee considered this formulation would reduce the burden on overloaded infusion services and enable easier access to treatments. The Committee considered that the treatment could be administered by a general practitioner or nurse or other primary health care practitioner working in their scope of practice. The Committee considered this would reduce time to treatment initiation.

11.17. The Committee noted that the SC formulation did not require a split first dose, and therefore required fewer overall administrations in the first year.

Cost and savings

11.18. The Committee noted that the uptake of IV ocrelizumab for PPMS has been lower than anticipated from use in people with RRMS. Although this reduced uptake could be due to infusion related services availability, it is more likely associated with reduced effectiveness of the drug for PPMS compared to RRMS. The adverse effect profile and reduced effectiveness contribute to the lower uptake.

11.19. The Committee considered that whilst there were eight funded treatments for RRMS, the main comparator for ocrelizumab would be natalizumab. The Committee noted that up to 50% of people are positive for the John Cunningham virus (JCV) and would not be able to use natalizumab.

11.20. The Committee considered 5% to 10% of people may transition to SC ocrelizumab from other treatments (including IV natalizumab) due to challenges with accessing infusion services, however up to 90% of those currently receiving IV ocrelizumab may transition to the SC formulation, if funded.

11.21. The Committee considered there may be a pool of individuals with PPMS who are not currently being treated in neurology clinics, due to poor treatment availability for PPMS in the past.

11.22. The Committee considered there may be an increase in the uptake of ocrelizumab for PPMS if SC ocrelizumab was funded. The Committee considered healthcare related costs would migrate from the hospital setting to the community setting for the administration of

treatment. The Committee noted that the administration of SC ocrelizumab may incur a cost to the individual from a GP practice.

Summary for assessment

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

Population	People with relapsing remitting multiple sclerosis (RRMS), and primary progressive multiple sclerosis (PPMS) who are eligible for intravenous ocrelizumab
Intervention	920 mg (40 mg/mL) ocrelizumab administered as one injection over ten minutes, every 6 months (with oral dexamethasone 20 mg and oral antihistamine administered shortly before injection to reduce potential risk of local or systemic reactions)
Comparator(s)	IV ocrelizumab administered as; First dose: (300 mg/10mL) ocrelizumab administered for 2.5 hours via intravenous infusion on day 1, and 2.5 hours on day 15. Subsequent doses: ocrelizumab administered for 3.5 hours via intravenous infusion that is reduced to 2 hours if well tolerated.
Outcome(s)	**Ocrelizumab subcutaneous versus intravenous administration** - No evidence of a difference in health benefits and risks between ocrelizumab SC and ocrelizumab IV - OCARINA II reported that ocrelizumab SC was non-inferior to ocrelizumab IV, with a similar safety profile (Unpublished data).
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. Benralizumab and mepolizumab (Fasenra and Nucala) - widening access to allow second-line treatment in patients with severe eosinophilic asthma

Application

12.1. The Committee reviewed a clinician application for widening access to benralizumab and mepolizumab for people with severe eosinophilic asthma (SEA) who experience waning efficacy from their current anti-IL5 biologic agent. The Committee noted that the application sought to allow switching between anti-IL5 biologic agents beyond 12 months (the timeframe enabled by the current funding criteria) and considered that this would effectively be funding a second-line treatment.

12.2. The Committee noted that Pharmac staff were in communication with the supplier of mepolizumab (GlaxoSmithKline NZ Limited [GSK]) prior to the PTAC meeting. GSK noted the applicant-provided evidence and confirmed there is little additional evidence they could provide to supplement this. GSK also provided a letter for PTAC's consideration.

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

Recommendation

12.4. The Committee **recommended** that the application to widen access to benralizumab and mepolizumab to allow second-line treatment in patients with severe eosinophilic asthma be funded with a **high priority**, subject to the following Special Authority criteria (changes from current criteria shown in **bold** and ~~strikethrough~~):

[BENRALIZUMAB/MEPOLIZUMAB]
Initial application — Severe eosinophilic asthma
Applications only from a respiratory physician or clinical immunologist **or any relevant practitioner on the recommendation of a respiratory physician or clinical immunologist**. Approvals valid for 12 months.
All of the following:

1. Patient must be aged 12 years or older; and
2. Patient must have a diagnosis of severe eosinophilic asthma documented by a respiratory physician or clinical immunologist; and
3. ~~Conditions that mimic asthma eg. vocal cord dysfunction, central airway obstruction, bronchiolitis etc. have been excluded; and~~
4. Patient has a blood eosinophil count of greater than 0.5 × 10^9 cells/L in the last 12 months; and
5. Patient must be adherent to optimised asthma therapy including inhaled corticosteroids (equivalent to at least 1000 mcg per day of fluticasone propionate) plus **a** long acting beta-2 agonist, or budesonide/formoterol as part of the single maintenance and reliever therapy regimen **(SMART)**, unless contraindicated or not tolerated; and
6. Either:
    - 6.1. Patient has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, where an exacerbation is defined as either documented use of oral corticosteroids for at least 3 days or parenteral corticosteroids; or
    - 6.2. Patient has received continuous oral corticosteroids of at least the equivalent of 10 mg per day over the previous 3 months; and
7. Treatment is not to be used in combination with subsidised [benralizumab/mepolizumab]; and
8. Patient has an Asthma Control Test (ACT) score of 10 or less. Baseline measurements of the patient's asthma control using the ACT and oral corticosteroid dose must be **recorded** ~~made at the time of application, and again at around 52 weeks after the first dose to assess response to treatment;~~ and
9. Either:
    - 9.1. Patient has not previously received an anti-IL5 biological therapy for their severe eosinophilic asthma; or
    - 9.2. Both:
        - ~~9.2.1. Patient was refractory or intolerant to previous anti-IL5 biological therapy; and~~
        - ~~9.2.2. Patient was not eligible to continue treatment with previous anti-IL5 biological therapy and discontinued within 12 months of commencing treatment.~~
        - **9.2.1. Patient has had an initial Special Authority approval for [mepolizumab/benralizumab] for severe eosinophilic asthma; and**
        - **9.2.2. Either:**
            - **9.2.2.1. Patient has experienced intolerable side effects; or**
            - **9.2.2.2. Both:**
                - **9.2.2.2.1. Patient has received insufficient benefit to meet the renewal criteria for [mepolizumab/benralizumab] for severe eosinophilic asthma; and**
                - **9.2.2.2.2. Patient must be adherent to optimised asthma therapy and has blood eosinophil count above the upper limit of normal.**

Renewal — Severe eosinophilic asthma
Applications only from a respiratory physician or clinical immunologist **or any relevant practitioner on the recommendation of a respiratory physician or clinical immunologist**. Approvals valid for 2 years.
Both:

1. An increase in the Asthma Control Test (ACT) score of at least 5 from baseline; and
2. Either:
    - 2.1 Exacerbations have been reduced from baseline by 50% as a result of treatment with [benralizumab/mepolizumab]; or
    - 2.2 Reduction in continuous oral corticosteroid use by 50% or by 10 mg/day while maintaining or improving asthma control.

12.5. In making this recommendation, the Committee considered:

12.5.1. the high health needs of people with SEA, including Māori, who are disproportionately impacted by severe asthma

12.5.2. that the low-quality retrospective evidence indicated a second-line biologic treatment is effective in people with SEA who have had insufficient benefit or waning efficacy from a first-line biologic.

12.6. The Committee recommended Pharmac staff seek advice from the Respiratory Advisory Committee regarding:

- the likely future growth and overall size of the treated population with SEA
- the likely split between first-line (with suboptimal benefit) vs second-line use (ie the proportion who would discontinue due to waning efficacy and switch to second-line treatment), if access were widened as proposed
- the proposed changes to the funding criteria, including if any restrictions to prescriber type are appropriate for targeting of treatment and the additions proposed to identify people who could be targeted for second-line biologic treatment at proposed special authority criterion 9.2.2.2
- whether any particular biomarkers that could aid biologic treatment selection for asthma are likely to be implemented internationally in the near future.

Discussion

Māori impact

12.7. The Committee discussed the impact of widening access to benralizumab and mepolizumab to allow second-line treatment in patients with SEA on Hauora Arotahi | Māori health areas of focus and Māori health outcomes. The Committee noted that there is good evidence of a higher health need in Māori, who experience a disproportionate impact from severe asthma and SEA and that this has been well documented in previous clinical advice records.

Populations with high health needs

12.8. The Committee discussed the health needs of people with SEA among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027. The Committee discussed the impact of widening access to benralizumab and mepolizumab to allow second-line treatment in this setting and made no other specific comments about these populations.

Background

12.9. The Committee noted that benralizumab and mepolizumab have been funded for severe eosinophilic asthma (SEA) subject to funding restrictions since August 2022 and April 2020, respectively.

12.10. The Committee noted that the funding criteria for use of these biologics in SEA intended to allow a switch due to intolerance or primary non-response. The Committee noted that switching between the two treatments due to waning efficacy (secondary non-response) was not the intent of the original listing but that this has effectively been able to occur within a 12 month period from starting treatment. The Committee considered that the 12 month timepoint for assessment of treatment benefit in the funding criteria was not necessarily supported by clinical evidence.

12.11. The Committee noted Pharmac has considered several proposals to widen access to these biologics for SEA by changing or removing criteria for the Asthma Control Test (ACT) and eosinophil count. Refer to the Application tracker for more information about these proposals (Application tracker - Eosinophilic asthma proposals).

Health need

12.12. The Committee noted that asthma is characterised by airflow obstruction, usually of the upper airways, with people experiencing symptoms of wheeze, chest tightness and shortness of breath. As symptom severity increases, people experience difficulty completing day-to-day activities and decreased quality of life. When someone has an acute exacerbation of asthma this can require high-dose corticosteroids and/or hospital admission for management. The Committee noted that eosinophilic asthma is a subtype of type 2 asthma in which elevated blood eosinophils are a marker of the condition.

12.13. The Committee noted that 5% to 10% of cases of asthma are severe and associated with ongoing poorly controlled symptoms with an increased frequency of acute exacerbations.

12.14. The Committee noted that asthma is well known to disproportionately affect Māori, which is noted in previous PTAC and Respiratory Advisory Committee meeting records (refer Application Tracker: severe asthma proposals). The Committee noted a study that reported that, of all people with asthma identified between 2011 and 2012 from the New Zealand HealthStat General Practice database and the National Minimum Dataset (NMDS), 21.6% were Māori from the overall group and 41.3% of those with severe eosinophilic asthma (SEA) were Māori (Shantakumar et al. Multidiscip Respir Med. 2020;15:662). The Committee considered that this study provided good evidence of a higher health need in Māori who experience a disproportionate impact from severe asthma and from SEA.

12.15. The Committee noted that individuals with SEA who receive a suboptimal response from biologic treatment will either remain on that biologic and require oral corticosteroids (OCS) or will discontinue the biologic due to not meeting the relatively stringent renewal criteria. Those who discontinue biologic treatment would receive best supportive care including OCS.

12.16. Members noted that the Shantakumar et al. 2020 study reported that the healthcare resource use (HCRU) for people with severe asthma accounted for about half of all HCRU for people with asthma; that health-related quality of life (QoL) was severely impaired for asthma patients and their caregivers; and that disease severity correlated with loss of productivity and with absenteeism.

12.17. The Committee noted that Pharmac staff had met with the clinician applicants, who described how logistical issues (ie due to constrained clinic and clinician capacity) meant that individuals with SEA were not always able to be assessed within the 12 month period.

12.18. The Committee noted that Pharmac has received several Named Patient Pharmaceutical Assessment (NPPA) and Special Authority waiver applications for individuals whose clinicians sought a funded switch between benralizumab and mepolizumab beyond 12 months. The Committee noted that most applications were approved, predominantly due to the reason for the request being an eosinophil count not meeting the required threshold due to prednisone usage (which is known to reduce the eosinophil count in this context).

Health benefit

12.19. The Committee noted that Australia (PBAC, based on a stakeholder meeting in 2018) and England/Wales (NICE, in 2019 and 2021 for benralizumab and mepolizumab, respectively) allow switching between biologics for SEA. However, in Canada, the CADTH was unable to provide a recommendation on sequencing of biologics for SEA in 2019 for both benralizumab and mepolizumab. The Committee was made aware that the most recent annual review by the CADTH concluded that further synthesis of the available evidence is unlikely provide more clarity on comparison of the efficacy and safety of the different biologics for severe asthma (CADTH, 2024).

12.20. The Committee considered that the key question here was the magnitude of benefit from a second-line biologic compared with a first-line biologic for SEA, and especially the incremental benefit that might be gained from a second-line biologic compared with remaining on a first-line biologic with suboptimal benefit. The Committee noted that the applicants provided evidence regarding switching between these two biologics in SEA but considered that to address the question it was appropriate to focus on outcomes from late switching (ie occurring after 12 months on first-line treatment).

12.21. The Committee noted that the minimal clinically important difference for the Asthma Control Test (ACT) is three and that this is commonly used to determine changes in asthma severity and gauge response to treatment (Respiratory Advisory Committee, October 2020).

12.22. The Committee noted a multicentre retrospective observational study of 68 people with SEA who were prescribed mepolizumab in 2015 at five centres for severe asthma in Italy

(Caminati et al. J Clin Med. 2023;12:1836). The Committee noted that the switch subgroup (n=30, of which half had incomplete data) were subsequently treated with benralizumab, while the non-switch subgroup (n=38) had a satisfactory response to mepolizumab and did not switch.

12.22.1. The Committee considered that the treatment switch was based upon reasonably stringent criteria (at least 50% reduction with respect to baseline in each of: OCS daily dose and exacerbation rate) and occurred after a median of 21 months (Q1-Q3: 12 to 24 months) of treatment with mepolizumab. The Committee noted that people who switched had higher baseline OCS dose, lower eosinophil count and were younger than those who did not.

12.22.2. The Committee noted that participants were followed up for median 31 months (IQR: 22 to 35 months). The Committee considered that the assessed outcomes (including the ACT score and exacerbation rate) in follow-up appeared improved post-switch compared with the pre-switch baseline, suggesting a benefit of second-line benralizumab in those experiencing late waning in efficacy from first-line mepolizumab. However, the Committee noted that the magnitude of these improvements appeared less than that experienced in the first six months in those who did not switch from mepolizumab (ie those receiving first-line treatment).

12.23. The Committee noted a multicentre retrospective study of 665 people with SEA treated with anti-IL-5 antibodies at six different university hospitals in Germany (Drick J Asthma Allergy. 2020:13:605-14). The Committee noted that 70 participants were in the switch subgroup and subsequently received benralizumab, 60 of which were included in the analysis as having received at least four months of benralizumab therapy, and that 48 of these people (80%) had received mepolizumab and 12 (20%) received reslizumab first-line. The Committee considered the evidence was not highly relevant given that the criteria for switching was not stringent, the switches occurred after a median of eight months (IQR: five to 15 months), and there was a short follow up duration of four months. However, the Committee considered the study indicated that some participants received a benefit from switching (ie reductions in OCS daily dose and exacerbation rate).

12.24. The Committee noted a retrospective single-centre study of 24 Japanese patients with SEA who received benralizumab in 2018-2019, of which 11 switched to receive benralizumab (Numata et al. BMC Pulm Med. 2020;20:207). The Committee noted that the switch subgroup previously received mepolizumab for median 21 months (range five to 35) and considered that the criteria leading to the switch were more relaxed than in the other studies reviewed, with most switches due to the interval between hospital visits. The Committee noted that there was no change in ACT or exacerbation rate post-switch compared with baseline in those who had previously received mepolizumab, although considered the sample size and permissive switch criteria limited the value of this study.

12.25. The Committee noted a retrospective single-centre study of 97 Japanese patients with severe asthma who received any biologics between 2009-2020 (Numata et al. J Asthma Allergy. 2021:14:609-18). The Committee noted that 34/97 (35%) switched to a second-line biologic (omalizumab, mepolizumab, benralizumab and/or dupilumab) and that the reasons for switching were similarly permissive as those in the previous study by the same first author. The Committee considered that while this study exemplified some of the evidence challenges in this context, it reflected an ability to switch frequently among multiple biologics in Japan and was not valid in the New Zealand context.

12.26. The Committee noted a letter by Kananagh et al. (Allergy. 2021;76:1890-3), which reported on a retrospective analysis of 33 people with SEA who switched from mepolizumab to benralizumab based on stringent criteria. The authors reported clinically significant improvements in exacerbation rate, OCS use, asthma control and quality of life scores after 48 weeks of benralizumab in most patients.

12.27. The Committee noted evidence from the multicentre XALOC1 trial which appeared to include both observational retrospective assessments and prospectively collected data for 1002 participants with SEA who received benralizumab (Jackson et al. Eur Respir J.

2024;64: 2301521). The Committee noted that 380 out of 1002 people (37.9%) were biologic-experienced, of whom 237 out of 380 people (62.4%) were on mepolizumab prior. The Committee noted that relative reductions in annualised exacerbation rate and the proportion who were exacerbation free at 48 weeks were slightly greater in those who were biologic-naïve compared with those who received mepolizumab prior (87.7% vs 69.0%, and 74.9% vs 60.4%, respectively). The Committee considered that XALOC1 was the most relevant evidence for determining the relative efficacy between biologic lines and that while benralizumab was efficacious in the first line, lesser efficacy would be expected in second line.

12.27.1. The Committee noted that XALOC1 used the ACT which, like a reduction in OCS dose or AER, provided indirect evidence of an improvement in QoL. The Committee considered it reasonable to infer that QoL improved with second-line mepolizumab, but the magnitude of this benefit was not as great as with first line benralizumab.

12.28. The Committee noted the following additional evidence for switching from a first-line to second-line biologic, predominantly from mepolizumab to benralizumab:

- Tavernier et al. Thorax. 2021;76:A1-A025(suppl_2).s87
- Caruso et al. Front Med (Lausanne). 2022:9:950883
- Corbridge et al. J Allergy Clin Immunol. 2024;153. Abstract Nr AB103. This study of a US claims database reporting outcomes in 89 people with severe asthma who received mepolizumab second-line, of which 28 had received first-line benralizumab. Members considered that this limited evidence suggested the sequence may provide similar outcomes as the reverse.
- Cartens et al. J Allergy Clin Immunol Pract. 2023; 11:2150-61.e4
- Jackson et al. J Allergy Clin Immunol Pract. 2022;10:1534-44.e4
- Chung et al. Ann Allergy Asthma Immunol. 2022;128:669-76
- Jackson et al. Eur Respir J. 2024;64:2301521
- Martinez-Moragon et al. BMC Pulm Med. 2021;21:417
- Langton et al. Respirology. 2023;28:1117-25
- Valery et al. J Allergy Clin Immunol. 2024;154:922-32

12.29. Members noted that the evidence suggests second-line biologic treatment suppresses blood eosinophils and that those people with low eosinophil counts did experience a therapeutic response, but people with a lesser degree of eosinophil suppression were more likely to experience a response to treatment.

12.30. The Committee considered that heterogeneity was high across the studies, with variation in the timing of switches, intervals between treatments, and in the indications for switching. Members noted that in some cases individuals appeared to switch while still receiving reasonable benefits from a first-line biologic. The Committee considered that the strength of this evidence was low, that there were limitations to the data and considered that the evidence base would not improve substantially with time. The Committee noted that most of the reviewed studies included people receiving mepolizumab who switched to benralizumab and that most studies were funded by AstraZeneca, the supplier of benralizumab.

12.31. Overall, the Committee considered that the evidence was from low quality, observational, retrospective studies and signalled that benralizumab and mepolizumab are efficacious as second-line biologics for SEA, but that the benefits are less than those obtained from use in a first-line setting. The Committee considered that this was a biologically plausible and somewhat expected conclusion, based on the known waning efficacy of monoclonal antibodies across other indications and the knowledge that disease which is non-responsive to treatment is subsequently more difficult to treat. The Committee concluded

there may be a benefit from late switching between these biologics for SEA at a population level.

12.32. The Committee considered that there was limited data to inform the efficacy and cost-effectiveness of switching between benralizumab or mepolizumab and any currently unfunded biologics (for example tezepelumab or dupilumab) for people with severe asthma. The Committee noted that the vast majority of the data related to mepolizumab and was made aware of three small retrospective studies reporting switch data for dupilumab (Mummler et al. J Allergy Clin Immunol Pract. 2021;9:1177-85.e4; Campisi et al. J Asthma Allergy. 2021;14:575-83; Numata et al. J Asthma Allergy. 2022:15:395-405). The Committee considered the evidence base likely to develop to a small extent over time, but that switch data for tezepelumab and research correlating biomarkers with treatment efficacy would help to inform consideration of switching between biologics, if such evidence was available in future.

Suitability

12.33. The Committee noted that following the initial doses, benralizumab has a longer dosing interval than mepolizumab. The Committee agreed with the clinician applicants' view that this would likely result in the preferential use of benralizumab over time.

Cost and savings

12.34. The Committee noted that this application would be expected to increase costs as it is effectively proposing funding for a second-line treatment and cost offsets would likely be small. [redacted]

12.35. The Committee considered that assumptions of the population proportions using treatments in subsequent lines were highly uncertain and would be increasingly so with any potential future changes in funding of asthma treatments.

12.36. The Committee considered it reasonable to assume a rate of treatment waning of 5% to 10% per year, based on overseas cohort evidence (Matucci et al. J Asthma 2023;60:158-66), but that this was highly uncertain. Members considered that treatment waning and switching could occur in a substantial proportion over time, noting that almost two thirds of biologic-experienced participants who received benralizumab in XALOC1 had received mepolizumab prior.

12.37. The Committee considered it reasonable to assume that improvements in health-related QoL and exacerbation frequency are slightly lower second-line compared to first line, based on the observational evidence available for outcomes which are likely to be highly correlated with QoL.

Funding criteria

12.38. Members considered that the blood eosinophil count criterion (targeting those with a blood eosinophil count of greater than 0.5 × 10^9 cells/L in the last 12 months) was likely not necessary, given the evidence indicates there is a benefit of second-line treatment with different levels of eosinophil suppression. The Committee noted Pharmac has considered several proposals to widen access to these biologics for SEA by changing or removing criteria for the ACT score and eosinophil count (see Application tracker - Eosinophilic asthma proposals).

12.39. The Committee recommended Pharmac staff seek advice from the Respiratory Advisory Committee regarding the proposed changes to the funding criteria, including if any restrictions to prescriber type are appropriate for targeting of treatment.

Summary for assessment

12.40. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for benralizumab and mepolizumab if widened access for second-line treatment were to be

funded in New Zealand for SEA. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

<table>
<tr><td>Population</td><td colspan="2">People with severe eosinophilic asthma who have not received sufficient benefit from first-line (1L) anti-IL5 biologic treatment (e.g. mepolizumab or benralizumab). This is without a specified time interval and includes both primary non-response, and secondary loss of response (waning).</td></tr>
<tr><td rowspan="2">Intervention</td><td colspan="2">Second-line (2L) biologic treatment with a different anti-IL5 medicine. The majority of people currently receiving biologics for eosinophilic asthma are receiving mepolizumab but this is expected to change over time:</td></tr>
<tr><td>Current (prevalent):
• Predominantly receiving mepolizumab 4-weekly as 1L
Then would switch to benralizumab 8-weekly as 2L</td><td>Future (prevalent + incident):
• Predominantly would commence on benralizumab 8-weekly as 1L (especially for high BMI)
Then would switch to mepolizumab 4-weekly as 2L</td></tr>
<tr><td>Comparator(s)</td><td colspan="2">Likely to be combination of:
- Some people continuing first-line biologic treatment (mainly mepolizumab) with suboptimal benefit (eg some reduction in OCS dose or exacerbations)
- Some people receiving standard non-biologic treatment (e.g. steroids) having discontinued biologics due to waning efficacy</td></tr>
<tr><td>Outcome(s)</td><td colspan="2">Based on the pivotal evidence of mepolizumab and benralizumab in a first-line setting – outcomes versus non-biologic treatment:
• Reduced exacerbations (per the original modelling)
• Reduction in oral corticosteroids
• Reduction in asthma symptoms
• Improved HRQoL
Uncertainty in:
- Whether the magnitude of benefit from a second-line biologic is smaller than the benefit from first-line, based on XALOC-1
- The extent to which switching biologics would provide incremental benefit, beyond continuing with a first-line biologic with suboptimal benefit</td></tr>
<tr><td colspan="3">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.</td></tr>
</table>

13. Atezolizumab (with chemotherapy) – for triple negative breast cancer, advanced or metastatic, PD-L1 expression over 1%

Application

13.1. The Committee reviewed the application for atezolizumab (with chemotherapy) for the treatment of advanced or metastatic triple negative breast cancer (TNBC) with a programmed death ligand 1 (PD-L1) expression over 1%.

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

Recommendation

13.3. The Committee **recommended** that the application for atezolizumab (with chemotherapy) for the treatment of advanced or metastatic triple negative breast cancer (TNBC) with a PD-L1 expression over 1% be **declined**.

13.4. In making this recommendation the Committee considered:

13.4.1. there was a lack of demonstrable overall survival (OS) and progression free survival (PFS) benefit associated with treatment with atezolizumab in combination with chemotherapy in this setting

13.4.2. that overall, clinical trial evidence was of high quality

13.4.3. clinical trials that included nab-paclitaxel in combination with atezolizumab were not relevant to the Aotearoa New Zealand (NZ) setting, as nab-paclitaxel is not currently funded. The Committee noted that the OS benefit analysis of the PD-L1 positive population was an exploratory analysis and considered overall the study reported an improvement in PFS and, in a *post hoc* analysis, reported individuals with PD-L1 staining of ≥1% had a likely, but formally unproven, OS benefit. The Committee considered there to be no health benefit, either in PFS or OS, in the addition of atezolizumab to paclitaxel, which is the currently funded option in NZ

13.4.4. treatment with atezolizumab was associated with an increase in the number of immune-mediated adverse events.

Discussion

Māori impact

13.5. The Committee discussed the impact of funding atezolizumab for the treatment of TNBC on Māori health areas of focus and Māori health outcomes. The Committee noted that breast cancer is one of Te Pātaka Whaioranga | Pharmac's Hauora Arotahi | Māori health areas of focus. The Committee noted the incidence of breast cancer in Māori women was 122.5 cases per 100,000 compared with 89.6 cases per 100,000 in non-Māori women (Te Whatu Ora Cancer Web Tool). Māori women are also diagnosed at a later stage in the disease process, and experience lower survival rates (at ten years) than non-Māori women (30,000 Voices: Te Rēhita Mate Ūtaetae – Breast Cancer Foundation National Register 2003-2020).

Populations with high health needs

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

13.6.1. Pacific peoples have higher rates of later stage breast cancer diagnosis and are more likely to experience delays to surgery than any other ethnic group. Pacific women have the lowest rates of survival from breast cancer of all ethnicities in New Zealand (Breast Cancer Foundation National Register 2003-2020).

Background

13.7. The Committee had reviewed and recommended for decline in November 2020 the application for atezolizumab (with chemotherapy) for the treatment of advanced or metastatic TNBC with a PD-L1 expression over 1%, due to evidence of a lack of OS benefit (compared with placebo plus nab-paclitaxel) in a key clinical trial, and limitations of the PD-L1 positive subgroup analysis.

13.8. The Cancer Treatments Advisory Committee (CTAC) reviewed the application in April 2021 and deferred making a recommendation, pending further published data of long-term follow-up from the IMpassion131 and IMpassion132 trials.

13.9. The supplier had provided further published follow up clinical trial data. Pharmac sought the Committee's review of the updated clinical trial evidence and potential health benefit of atezolizumab in this population.

Health need

13.10. The Committee noted individuals with advanced or metastatic TNBC have poorer outcomes in comparison to people with other types of breast cancer (Hsu et al. Sci Rep. 2022;12:729).

13.11. The Committee considered there is evidence of a survival benefit from the use of chemotherapy, including cisplatin in combination with paclitaxel, in this population. The Committee considered that studies investigating the combination benefit of other immune checkpoint inhibitors in combination with chemotherapy have shown clinical benefit for individuals with metastatic or advanced TNBC. The Committee noted, based on this evidence, that pembrolizumab has been funded in New Zealand for the treatment of people with advanced TNBC with a Combined Positive Score (CPS) score ≥ 10 since October 2024.

Health benefit

13.12. The Committee noted Emens et al. Ann Oncol. 2021;32:983-93, which reported the final OS analysis of the IMpassion130 trial:

13.12.1. Median OS in the intention to treat (ITT) population was 21.0 months [95% CI 19.0-23.4 months] with atezolizumab plus nab-paclitaxel (A + nP), and 18.7 months (95% CI, 16.9-20.8 months) with placebo plus nab-paclitaxel (P+ nP) P + nP [stratified hazard ratio (HR), 0.87; 95% CI, 0.75-1.02; P = 0.077].

13.12.2. Exploratory prespecified subgroup analysis in the PD-L1 IC-positive population reported a median OS of 25.4 months (95% CI, 19.6-30.7 months) with A + nP (n = 185) and 17.9 months (95% CI, 13.6-20.3 months) with P + nP (n = 184; stratified HR, 0.67; 95% CI, 0.53-0.86 months).

13.12.3. The Committee noted that the OS benefit analysis of the PD-L1 positive population was an exploratory analysis, and the statistical analysis plan did not allow for a formal analysis.

13.12.4. The Committee considered overall the study reported an improvement in PFS and, in a *post hoc* analysis, reported individuals with PD-L1 staining of ≥1% had a likely, but formally unproven, OS benefit.

13.12.5. The Committee noted that nab-paclitaxel is not funded in New Zealand. Therefore, the Committee considered that whilst the evidence was of high quality it was not relevant to the New Zealand context.

13.13. The Committee noted Miles et al. Ann Oncol. 2021;32:994-1004, which reported the results of the IMpassion 131 trial, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. The study reported the following results:

13.13.1. Primary PFS analysis: adding atezolizumab to paclitaxel did not improve investigator-assessed PFS in the PD-L1-positive population [HR 0.82, 95% CI 0.60-1.12; P = 0.20; median PFS 6.0 months with atezolizumab-paclitaxel versus 5.7 months with placebo-paclitaxel].

13.13.2. Final OS results showed no statistically significant difference between arms (HR 1.11, 95% CI 0.76-1.64; median 22.1 months with atezolizumab-paclitaxel versus 28.3 months with placebo-paclitaxel in the PD-L1-positive population).

13.13.3. The Committee noted 45% of the trial population were PD-L1 positive.

13.13.4. The Committee noted the difference in outcomes between the IMpassion130 and 131 trials and considered the reasoning behind this remained unclear. The

Committee noted that unlike nab-paclitaxel, paclitaxel administration also requires the use of corticosteroids.

13.13.5. The Committee considered that this trial more accurately reflected the New Zealand setting, where paclitaxel is funded.

13.13.6. The Committee considered the trial to be of high quality that included a large sample population. The Committee considered there to be no health benefit, either in PFS or OS, in the addition of atezolizumab to paclitaxel.

13.14. The Committee noted Dent Ann Oncol. 2024;35:630-42, which reported the results of the Impassion132 trial; a double blind randomised phase III trial in people with advanced TNBC relapsing <12 months after last chemotherapy dose (anthracycline and taxane required) or surgery for early TNBC. The study reported the following results:

13.14.1. The OS hazard ratio was 0.93 (95% CI 0.73-1.20, P = 0.59; median OS 11.2 months with placebo versus 12.1 months with atezolizumab). mITT and subgroup results were consistent with the primary analysis and 95% CIs for the HR point estimates crossed 1 in all subgroups analysed.

13.14.2. As the primary endpoint did not reach statistical significance, prespecified secondary endpoints were not formally tested. Median PFS was 4 months across treatment arms and populations. Unconfirmed objective response rate (ORR) was 28% (95% CI 21-36]) with placebo versus 40% (95% CI 32-48) with atezolizumab.

13.14.3. The Committee noted that the trial did not report an OS benefit for atezolizumab compared to chemotherapy alone (HR 0.93, 95% CI 0.73-1.20, P = 0.59).

13.14.4. The Committee noted that the chemotherapy used in the trial, carboplatin in combination with gemcitabine, is a combination that is currently used in New Zealand and would be a relevant comparator.

13.15. The Committee noted Vishnu et al. BMC Cancer. 2022;22:1139, which reported the results of a meta-analysis of six randomised controlled trials. The Committee noted that the meta-analysis did not report an OS advantage, however there was a PFS gain for combined atezolizumab and nab-paclitaxel (HR 0.72, 95% CI [0.59, 0.87], p=0.0006) and an ORR gain (RR 1.25, 95% CI [0.79, 1.01] p<0.00001) although this was based on the results of a single positive trial. The Committee considered the meta-analysis was classified as high quality of evidence.

13.16. The Committee noted the following publications:

- Alimohammadi et al. Curr Pharm Des. 2023;29:2461-76
- Huo et al. Crit Rev Oncol Hematol. 2021:168:10353
- Leung et al. Expert Opin Drug Saf. 2023;22:243-52.

13.17. The Committee considered overall there was no evidence to support the use of atezolizumab (with chemotherapy) for the treatment of advanced or metastatic TNBC with a PD-L1 expression over 1%, with no evidence of improvements in either PFS or OS in the New Zealand context.

Suitability

13.18. The Committee considered that the addition of atezolizumab to chemotherapy would increase the frequency of infusions and this may result in a burden on infusion services. The increased frequency of administration would result in additional travel for the individual and/or their whānau and caregivers. Time spent travelling to access health care services impacts other activities for the person such as paid employment and time with family and whānau.

Cost and savings

13.19. The Committee noted in IMpassion130 that immune-mediated adverse events of special interest were reported in 58.7% and 41.6% of individuals treated with A + nP and P + nP, respectively. The Committee considered therefore the addition of atezolizumab increased the number of immune related adverse events, which can be complicated to manage.

Summary for assessment

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

Population	People with inoperable locally advanced or metastatic triple-negative breast cancer whose tumour tests positive for a PD-L1 expression (>1%), without prior treatment with a PD-L1 inhibitor.	
	With a CPS score of ≥10 and therefore eligible for pembrolizumab.	With a CPS score of <10 and are ineligible for pembrolizumab
Intervention	Atezolizumab, 840 mg administered every two weeks. Administered in combination with either: • paclitaxel 90mg/m 2 on days 1, 8 and 15, every 28 days, or: • gemcitabine 1000mg/m2 and carboplatin AUC on days 1, 8, every 21 days Treatment continued until disease progression, or unacceptable toxicity.	
Comparator(s)	Pembrolizumab, 200mg administered every three weeks. Administered in combination with either: • paclitaxel 90mg/m^2 on days 1, 8 and 15, every 28 days, or: • gemcitabine 1000mg/m^2 and carboplatin AUC on days 1, 8, every 21 days Treatment continued until disease progression, or unacceptable toxicity, or a maximum of 35 administrations.	Funded chemotherapy, comprising either: • paclitaxel 90mg/m^2 on days 1, 8 and 15, every 28 days, or: • gemcitabine 1000mg/m2 and carboplatin AUC on days 1, 8, every 21 days
Outcome(s)	No evidence of an incremental health benefit or risks associated with atezolizumab-chemotherapy compared to pembrolizumab-chemotherapy.	No specific evidence identified to inform the health benefit associated with atezolizumab-chemotherapy among cases with a CPS of <10 but a PD-L1 expression of >1%.
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.		