PHARMAC
TE PĀTAKA WHAIORANGA

Pharmacology and Therapeutics
Advisory Committee

Objective advice to Pharmac

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 16 May & 17 May 2024

1. Present:

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

Apologies:
Bruce King

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
8.1.3	Sildenafil for erectile dysfunction subject to Special Authority criteria	Medium Priority

8.1.4	Tadalafil for erectile dysfunction subject to Special Authority criteria	Low Priority
8.2.1	Bevacizumab for second-line treatment of high-risk advanced ovarian cancer	Decline
8.3.3	Deflazacort for the treatment of Duchenne muscular dystrophy (DMD)	Decline
9.3	Selexipag for the treatment of pulmonary arterial hypertension subject to Special Authority criteria	High Priority
10.3	Macitentan for the treatment of pulmonary arterial hypertension	Decline
10.5	Macitentan for the treatment of porto-pulmonary hypertension	Low Priority
11.3	Pembrolizumab in addition to chemotherapy with bevacizumab for the treatment of persistent, recurrent or metastatic cervical cancer	Decline
11.5	Pembrolizumab in addition to chemotherapy, without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer	High Priority
12.3	Lenvatinib in combination with pembrolizumab for the treatment of renal cell carcinoma subject to Special Authority criteria	Low Priority
12.4	Axitinib in combination with pembrolizumab for the treatment of renal cell carcinoma subject to Special Authority criteria	Medium Priority

4. Record of PTAC meeting held 15 February & 16 February 2024

4.1. The Committee reviewed the record of the PTAC meeting held on 15 February & 16 February 2024

4.2. The Committee accepted the record.

5. Action Points

5.1. There are no current action points.

6. Pharmac Update

6.1. The Committee noted the Pharmac Update.

7. Specialist Advisory Committee Records

9 June 2023 Dermatology Specialist Advisory Committee Record

7.1. PTAC reviewed the records of the Dermatology Specialist Advisory Committee held on 9 June 2023.

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

12 & 13 October 2023 Cancer Treatments Specialist Advisory Committee Record

7.3. PTAC reviewed the records of the Cancer Treatments Advisory Committee (CTAC) held on 12 & 13 October 2024.

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

7.5. PTAC noted the Advisory Committee's recommendation that netupitant/palonosetron for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic anti-cancer treatments (MEC) be declined. PTAC also noted the Advisory Committee's medium priority recommendation for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic anti-cancer treatments. PTAC noted the updated guidelines that if an individual experiences severe vomiting and nausea during their first cycle with a moderate chemotherapeutic agent then the regime would be categorised as a highly emetogenic regime and would be eligible for netupitant/palonosetron for subsequent cycles if funded.

27 October 2023 Special Foods Specialist Advisory Committee Record

7.6. PTAC reviewed the records of the Special Foods Advisory Committee held on 27 October 2023.

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

10 October 2023 Immunisation Specialist Advisory Committee Record

7.8. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee held on 10 October 2023.

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

9 November 2023 Immunisation Specialist Advisory Committee Record

7.10. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee held on 9 November 2023.

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

30 May 2023 and 12 December 2023 COVID-19 Treatments Advisory Group Record

7.12. PTAC reviewed the records of the COVID-19 Treatments Advisory Group held on 30 May 2023 and 12 December 2023.

7.13. PTAC noted the records including the Advisory Group's recommendations.

8. Matters Arising

8.1. PDE5 inhibitors for erectile dysfunction - clarification of next steps (P-002034)

Application

8.1.1. The Committee reviewed the information provided for PDE5 inhibitors for erectile dysfunction.

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

Recommendation

8.1.3. The Committee **recommended** that access to sildenafil be widened for erectile dysfunction with a **medium priority** subject to the following Special Authority criteria:

> **Initial application — (erectile dysfunction)** from any relevant practitioner. Approvals valid without further renewal unless notified where person has erectile dysfunction.

8.1.4. The Committee **recommended** that tadalafil be listed for erectile dysfunction with a **low priority** subject to the following Special Authority criteria:

> **Initial application — (erectile dysfunction)** from any relevant practitioner. Approvals valid without further renewal unless notified where person has erectile dysfunction.

8.1.5. The Committee considered the following in making these recommendations:

- The health need attributable to erectile dysfunction is unlikely to vary according to the aetiology
- Overall, patient perception of health need decreases with age
- Health benefits of sildenafil and tadalafil in erectile dysfunction are similar, but the usefulness of treatment varies by the underlying cause of the erectile dysfunction
- The pharmaceutical cost of sildenafil was substantially lower than for tadalafil.

Discussion

Māori impact

8.1.6. The Committee discussed the impact of funding PDE5 inhibitors for the treatment of erectile dysfunction on Māori health areas of focus and Māori health outcomes. The Committee considered that while no specific information for Māori with erectile dysfunction was reviewed at this meeting, this population may experience barriers to accessing healthcare.

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

8.1.7. The Committee discussed the impact of funding PDE5 inhibitors for the treatment of erectile dysfunction on priority populations. The Committee considered that whilst there was no specific information for Pacific peoples with erectile dysfunction, this population may experience many of the same barriers to access as Māori.

Background

8.1.8. The Committee noted its previous consideration of PDE5 inhibitors for erectile dysfunction in people with spinal cord injury (May 2014). The Committee also noted it's previous comment that with other causes of erectile dysfunction, such as diabetes, hypertension, multiple sclerosis or damage after prostate surgery, could have a similar case for funding. The Committee noted that this was re-iterated when it considered PDE5 inhibitors following treatment for prostate cancer treatment (February 2024).

Health need

8.1.9. The Committee considered that erectile dysfunction increases with age with an estimated prevalence of 18% at 50 years and 37% at 70 years (Feldman et al. J Urol. 1994;151:54-61). The Committee noted a New Zealand survey documenting local experience was consistent with other surveys on erectile dysfunction (Quilter et al. J Sex Med. 2017;14:928-36). The Committee noted that there was a poor response rate in this survey and the distribution of respondents were more likely to be ethnically European, have a long-term partner, have higher education, or be living rurally. The Committee considered that for some men in New Zealand there would be whakamā (shame or embarrassment) surrounding the diagnosis or treatment of this condition that could lead to delays.

8.1.10. The Committee noted that health-related quality of life impacts of erectile dysfunction may decrease with age; younger people experience greater impacts than older people.

The Committee noted the partner's perception of the impact of erectile dysfunction may differ from the affected person's view.

8.1.11. The Committee noted that sildenafil is widely used for erectile dysfunction in the community as it is available on prescription and pharmacist only supply. The Committee noted that current estimates on community usage of sildenafil for erectile dysfunction outside of the funded indications were not available.

8.1.12. The Committee noted that erectile dysfunction can have many aetiologies including cardiovascular, neurogenic, hormonal, psychological, trauma from surgery or injury, drugs or medications. The Committee considered that risk factors for erectile dysfunction include age over 40 years, diabetes, cardiovascular disease, high cholesterol, hypertension, BMI >25, depression, physical inactivity, smoking and/or drug and alcohol abuse. The Committee again noted its previous advice that people with different causes of erectile dysfunction who are eligible for funded treatment likely have a similar health need and therefore a case for funded treatment.

8.1.13. The Committee considered that assessing the onset, duration, severity, progression and factors relieving and aggravating erectile dysfunction as well as the modifiable and non-modifiable risks and if the person has a stable partner, then appropriately involving their partner before recommending treatment with a PDE5 inhibitor was the ideal but was unlikely to be realistic in most cases.

Health benefit

8.1.14. The Committee noted that the diagnostic tool commonly used to assess severity of erectile dysfunction was the International Index of Erectile Function (IIEF) questionnaire. The Committee noted that this tool consisted of 15 questions resulting in an overall score relating to the severity of erectile dysfunction. The Committee noted that it was common for trials to focus on single questions (typically question 3 or 4) or the overall score.

All comers

8.1.15. The Committee noted a 12-week dose escalation followed by a 32 week open-label extension with 329 participants (Goldstein et al. N Engl J Med 1998; 338:1397-1404). The Committee noted that successful intercourse was reported in 69% of the sildenafil group and 22% of the placebo group. The Committee noted a dose response relationship was reported across the 25 mg, 50 mg and 100 mg groups. The Committee noted that common adverse events headache, flushing and dyspepsia at a rate of up to 18%.

8.1.16. The Committee noted a 3 week on demand trial with a minimum 4 trial occasions with 179 participants (Padma-Nathan et al. Int J Impot Res. 2001;13:2-9). The Committee noted tadalafil had reported similar results to the sildenafil. The Committee noted that tadalafil significantly improved IIEF Q3 scores at all doses vs placebo ($P \leq 0.003$), tadalafil also significantly improved IIEF Q4 scores in all but the 2 mg group ($P \leq 0.0003$).

Diabetes

8.1.17. The Committee noted the following studies assessing sildenafil in people with diabetes:

8.1.17.1. Vardi et al. Cochrane Database of Reviews. 2007

8.1.17.2. Boulton et al. Diabetologica. 2001; 44: 1296-1301

8.1.17.3. Blonde. Curr Med Res Opin. 2006;22: 2111-20

8.1.17.4. El-Sakka et al. Eur Urol. 2004;46:503-9

8.1.17.5. Bronwyn et al. Diabetes Care 2003;26:279–84

8.1.17.6. Price et al. Diabetic Medicine. 1998; 15:821-5

8.1.17.7. Safarinejad et al. J Diabetes Complications. 2004;18:205-10

8.1.18. The Committee noted a randomised flexible dose-escalation study in people with type 1 diabetes (90%) with a mean age of 57 years (Rendell et al. JAMA. 1999;281:421-26).

The Committee noted that the participants had to have stable diabetes management and a partner for at least 6 months. The Committee noted that 93% of participants escalated their dose to 100 mg. The Committee noted that 56% of participants experienced improved erections with sildenafil and 10% with placebo. The Committee noted that at least one successful erection was achieved in 61% of the sildenafil group and 22% of the placebo group.

8.1.19. The Committee noted that most of the publications are over 20 years old and overall sildenafil was effective, but the response was less than all-comers studies (eg Goldstein et al. 1998). The Committee considered that caution is required with the use of sildenafil in those with ischaemic heart disease.

8.1.20. The Committee noted that in a randomised trial successful intercourse completion increased to 50.3% among men receiving tadalafil compared with small improvements in those randomised to placebo (Carson et al. Urology. 2005; 65:353-59). The Committee noted that there were no cardiovascular events or effects were reported, but those at higher risk were excluded from studies.

8.1.21. The Committee also noted the following studies assessing tadalafil in people with diabetes:

8.1.21.1. Vardi et al. Cochrane Database of Reviews. 2007

8.1.21.2. Fonseca et al. Diabetologia. 2004; 47:1914-23

8.1.21.3. Hatzichristou et al. Diabetic Medicine. 2008;25:138-46

8.1.21.4. Sadenz de Tejada et al. Diabetes Care 2002;25:2159–64

8.1.21.5. Srdan et al. Vojnosanitetski pregled. 2007;64:399-404

8.1.22. The Committee noted that these publications were also older (>18 years) but considered that overall people treated with tadalafil had similar response to those treated with sildenafil.

8.1.23. The Committee considered that in most of the studies that participants were not using insulin to manage their diabetes; the impact of PDE5 on those with insulin-dependent diabetes mellitus (IDDM) has not been comprehensively assessed and those patients may have greater cardiovascular compromise, such as ischaemic heart disease. The Committee noted that diabetes screening programmes now also screen for erectile dysfunction.

Hypertension

8.1.24. The Committee noted the following studies assessing sildenafil in people with hypertension:

8.1.24.1. Park et al. J Sex Med. 2008; 5:2405-13

8.1.24.2. Pickering et al. Am J Hypertens. 2004; 17:1135-42

8.1.24.3. Albuquerque et al. Int Braz J Urol. 2005;31:342-53

8.1.25. The Committee considered that the results were similar to all comers (eg Goldstein et al. 1998) in terms of effect. The Committee considered that these effects were not related to the number of anti-hypertensives. The Committee considered that overall there was an increased incidence of cardiovascular adverse effects including chest pain, hypotension and palpitations, consistent with an increased incidence of cardiovascular compromise.

8.1.26. The Committee noted a publication using data from 14 randomised control trials comparing people taking and not taking thiazides and the effect of tadalafil (Kloner et al. Int J Impot Res. 2005;17:450-4). The Committee noted that mean per-patient change from baseline for SEP2 in severe erectile dysfunction patients was 50.8% in thiazide users compared to 53.6% in non-thiazide users. The Committee considered that tadalafil was effective whether people were taking thiazides or not.

Multiple sclerosis (MS)

8.1.27. The Committee noted a systematic review of two trials assessing the use sildenafil for erectile dysfunction in people with multiple sclerosis (Xiao et al. Cochrane Database of Systemic Reviews. 2012). The Committee noted that people taking sildenafil were unlikely to improve their ability to achieve and maintain an erection and achieve vaginal penetration (relative risk (RR)1.28, 95% CI 0.92, 1.78) or complete intercourse (RR 1.38, 95% CI 1.00, 1.90). The Committee noted that one trial showed sildenafil citrate is effective in quality of life improvement, while the other trial did not find a difference. The Committee noted that two people suffered serious adverse events: one with coronary artery disease requiring triple bypass surgery and one with a cerebrovascular accident. The Committee considered that there is limited evidence to support sildenafil citrate as an effective treatment for ED in patients with MS.

8.1.28. The Committee noted that an open label trial of tadalafil in men with erectile dysfunction. The Committee noted that these men had more complex disease with mobility and neurological issues, spasticity, bladder bowel dysfunction, fatigue, relationship breakdown, with onset at 20-40 years rather than 57 years. The Committee noted that people who responded had some improvement at all follow-up compared with baseline on the erectile domain and overall sexual satisfaction scores. The Committee considered that clinical significance is unlikely due to the small absolute improvement. The Committee noted that statistical improvement sexual life, family life, and partner relationship compared with baseline, but that the baseline low, improvement was small and clinical significance was not clear.

8.1.29. The Committee considered that for people with multiple sclerosis, PDE5 inhibitors were less effective than in other populations.

Cost and savings

8.1.30. The Committee considered that there is little information available for discontinuation rates for many of the diseases associated with erectile dysfunction. The Committee considered it might be reasonable to assume that the discontinuation rate of PDE5 inhibitors would be 45% at 18 months based on an observational study in the prostate cancer treatment setting previously reviewed in February 2024 (Souverein et al. Int J Impotence Res. 2002;14: 259-265). The Committee considered however that the study should be interpreted with clinical context (eg, there is some recovery of erectile function after prostate surgery, further diseases or drugs that could negatively affect function, changing social circumstances, and importance of erectile function diminishes in many with age).

8.1.31. The Committee considered that funded access to PDE5 inhibitors may result in an in people attending the GP to start treatment, and receive additional monitoring of comorbid conditions, complications, effectiveness and dose scaling.

8.1.32. The Committee considered that funding PDE5 inhibitors could result in a reduction in pharmacist consults for sildenafil as people would likely prefer treatment from the GP, as it would be publicly funded.

8.1.33. The Committee considered that an increase in the number of people attending the GP could mean that there could be opportunistic screening for other conditions and management of other long-term conditions may be undertaken more regularly.

Funding criteria

1.1. The Committee considered that the proposed criteria would appropriately target access to those with erectile dysfunction. The Committee noted that due to other funded indications Special Authority criteria would be required to continue to target funding to specific indications.

Summary for assessment

8.1.34. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for

PDE5 inhibitors (sildenafil or tadalafil) if it were to be funded in New Zealand for erectile dysfunction. 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 ED due to any cause, for whom a PDE5-inhibitor is a suitable treatment option.
Intervention	Sildenafil tablets, at a starting dose of 50mg taken approximately one hour before sexual activity. • An estimated average frequency of use of 2.4 times per week (Sairam et al. BMC Urology. 2002;2: 4) • An estimated 80% of treated individuals, who experience a response to sildenafil, may require a dose escalation to 100mg (Kedia et al. Urology. 1999;54:308-12). • Taken indefinitely provided the treatment remains safe and appropriate and the individual is benefiting from treatment. Discontinuation rate on PDE5-inhibitors estimated to be roughly 45% at 18 months (Souverein et al. Int J Impotence Res. 2002;14: 259-265). The applicability of this estimate to the target population is uncertain.
Comparator(s) (NZ context)	No funded PDE5-inhibitor treatment.
Outcome(s)	Treatment response • PDE5-inhibitor treatment is associated with a higher international Index of Erectile Function – Erectile Function domain score compared to placebo, among people with ED (mean diff = 6.6, 95% CI 5.2, 7.9) (Vardi et al. Cochrane Database of Reviews. 2007). • The efficacy of PDE5-inhibitors for the treatment of ED is assumed to be similar across ED due to different causes. • A class effect of efficacy between PDE5-inhibitors is assumed. Improved health-related quality of life • Improved erectile function, as measured by the International Index of Erectile Function, is associated with improved health-related quality of life (Smith et al. Clin Drug Investigation. 2012;25:99-105)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

8.2. Bevacizumab for 2L treatment of ovarian cancer - consultation feedback (P-001803)

Recommendations

8.2.1. The Committee **recommended** the application for bevacizumab for second-line treatment of high-risk advanced ovarian cancer be **declined**. In making this recommendation, the Committee considered:

- the high health need of people with recurrent or resistant ovarian cancer;
- bevacizumab provides a small beneficial effect on PFS, however there is little to no improvement in overall survival for people with recurrent or resistant ovarian cancer;
- the high cost to the health system of bevacizumab, compared to the marginal benefits in treating recurrent or resistant ovarian cancer;

- there are rare but important adverse effects associated with bevacizumab.

Discussion

8.2.2. The Committee noted Pharmac consulted on a proposal to decline a funding application for bevacizumab for second-line treatment of high-risk advanced ovarian cancer. The Committee noted Pharmac had received feedback that included additional evidence not previously considered and that it sought advice from the Committee regarding this.

8.2.3. The Committee noted Pharmac had ranked a funding application for bevacizumab as a first-line treatment for advanced high-risk ovarian cancer, in combination with platinum-based chemotherapy, on its Options for Investment list.

8.2.4. The Committee noted that second-line treatment includes resistant disease, where recurrence occurs within 6 months of first-line platinum chemotherapy, and recurrent disease, where recurrence occurs after 6 months of first-line platinum chemotherapy. The Committee considered there is a high health need for women with recurrent or resistant ovarian cancer.

8.2.5. The Committee noted evidence supporting the use of bevacizumab in the resistant or recurrent setting.

8.2.5.1. The Committee noted the OCEANS trial, a randomised, placebo controlled phase three trial evaluating the efficacy and safety of bevacizumab combined with gemcitabine and carboplatin for people with platinum-sensitive recurrent ovarian cancer. (Aghajanian et al. Gynecol Oncol. 2015;139(1):10-6). The Committee noted the trial reported an absolute median progression free survival (PFS) difference of 4 months (HR 0.484; 95% CI 0.388, 0.605) and no statistically significant difference in overall survival (OS) (absolute difference 0.7 months, HR 0.95; log-rank p 0.65).

8.2.5.2. The Committee noted the GOG-0213 trial, an open-label, randomised, phase 3 trial evaluating the addition of bevacizumab to chemotherapy (comprising of paclitaxel and carboplatin) in adult women with recurrent measurable or evaluable relapsed epithelial ovarian, primary peritoneal or fallopian tube cancer (Coleman et al. Lancet Oncol. 2017;18(6):779-91). The Committee noted the trial reported an absolute median PFS difference of 3.4 months (HR 0.628; 95% CI 0.534, 0.739) and no statistically significant difference in OS in the intention to treat (ITT) population (absolute difference 4.9 months, HR 0.829; 95% CI 0.683, 1.005). The Committee noted after correction for admitting patients with the incorrect treatment-free interval (n=45), a statistically significant OS benefit was observed (HR 0.823; 95% CI 0.680, 0.996).

8.2.5.3. The Committee noted the MITO 16 trial, an open-label, randomised phase 3 trial evaluating the addition of bevacizumab to carboplatin-based doublet chemotherapy in adult women who previously received first-line platinum-based therapy including bevacizumab, and had recurrent stage IIIB-IV ovarian cancer (Pignata et al. Lancet Oncol. 2021;22(2):267-76). The Committee noted the trial reported an absolute median PFS difference of 3 months (HR 0.51; 95% CI 0.41, 0.65). The Committee noted OS was not reported.

8.2.5.4. The Committee noted the AURELIA trial, an open-label, randomised phase 3 trial evaluating the addition of bevacizumab to chemotherapy for platinum-resistant recurrent ovarian cancer (Pujade-Lauraine et al. J Clin Oncol. 2014;32(35):4025) The Committee noted the trial reported an absolute median PFS difference of 3.3 months (HR 0.48; 95% CI 0.38, 0.60) and no statistically significant difference in overall survival (absolute difference 3.3 months, HR 0.85; 95% CI 0.66, 1.08).

8.2.5.5. The Committee noted the JGOG 3023 trial, an open-label, phase II trial evaluating the addition of bevacizumab to chemotherapy in people with relapsed ovarian cancer after completing first-line platinum-based

chemotherapy in combination with bevacizumab (Shoji et al. Cancer Sci. 2022;113(1):240-50). The Committee noted a median PFS difference of 0.9 months (HR 0.54; 95% CI 0.32, 0.90) and no statistically significant difference in OS (absolute difference 4 months, HR 0.67; 95% CI 0.38, 1.17).

8.2.6. The Committee noted that additional evidence was submitted evaluating the use of bevacizumab in low grade serous ovarian cancer, advanced mucinous ovarian cancer and advanced clear cell ovarian cancer.

8.2.6.1. The Committee noted MITO 22, a retrospective observational study evaluating bevacizumab in patients with recurrent low grade serous ovarian cancer after first line platinum based chemotherapy (Musacchio et al. Gynecol Oncol. 2023;172:72-7) The Committee noted the trial reported an absolute PFS difference of 25.9 months but did not report data on OS. The Committee noted matching was suboptimal, particularly in relation to residual disease.

8.2.6.2. The Committee noted GOG-0241, a randomised factorial, phase 3 trial evaluating the addition of bevacizumab to platinum-based chemotherapy in people with mucinous epithelial cancer (Gore et al. Gynecol Oncol. 2019;153:541-48). The Committee noted that the cohort included people receiving both first- and second-line treatment. The Committee noted the trial was highly confounded with less than 50% of tumours being primary mucinous tumours upon central pathology review. The Committee noted there was no difference in OS survival reported (HR 1.04, 95% CI 0.51, 2.10) even after correction for true mucinous ovarian cancer cases (HR 1.08, 95% CI 0.30, 3.84).

8.2.6.3. The Committee noted a conference abstract (Seki et al. JCO. 2022;40:5502), reporting a historical control cohort analysis comparing patients with advanced clear cell ovarian cancer before and after the approval/funding of bevacizumab. The Committee noted a median OS difference of 16.7 months was reported (p=0.09), however matching was imperfect with completeness of resection being the strongest predictor of outcome.

8.2.6.4. The Committee considered that these groups were outside the scope of the funding application being considered. The Committee noted these were retrospective studies of very low quality that demonstrated some benefit of bevacizumab in rarer forms of ovarian cancer, however, were heavily confounded by imperfect matching of patients.

8.2.7. The Committee considered that the trial data indicates there may be a very marginal progression-free survival benefit from bevacizumab in recurrent or resistant ovarian cancer when added to chemotherapy. In addition to this, the Committee considered that the totality of the data indicated there was little to no improvement in overall survival from bevacizumab in this setting. The Committee considered that the evidence did not warrant funding for any prevalent group that may exist should bevacizumab be funded for first-line treatment.

8.2.8. The Committee noted the safety profile of bevacizumab. The Committee noted that there are rare, but significant risks associated with treatment, notably grade 3 to 5 gastrointestinal perforation and fistulae. The Committee considered that these side effects, while uncommon can be severe.

8.3. Deflazacort - Duchenne muscular dystrophy - new evidence from FOR-DMD study (P-001458)

Application

8.3.1. The Committee reviewed new evidence from the FOR-DMD study for deflazacort for the treatment of Duchenne muscular dystrophy (DMD). The Committee also reviewed patient perspectives on deflazacort provided by Muscular Dystrophy New Zealand (MDNZ).

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

Recommendation

8.3.3. The Committee reaffirmed its previous recommendation that the application for deflazacort for DMD be **declined**.

8.3.4. In making this recommendation, the Committee considered:

- The high unmet health needs of people with DMD in New Zealand, and the high level of care required from their whānau
- The FOR-DMD trial provided high quality evidence showing no significant differences in efficacy or adverse effect profiles between daily prednisone and daily deflazacort treatment regimens
- The comparable suitability between prednisone/prednisolone and deflazacort
- The potential costs and savings to the health system if deflazacort were to be funded.

8.3.5. The Committee requested that the Neurological Advisory Committee consider a horizon scan of alternative treatment options for DMD, including alternative corticosteroid preparations for those in whom prednisone is not tolerable, and other newer treatments in development or approved in overseas settings, at a future meeting.

Discussion

Māori impact

8.3.6. The Committee discussed the impact of funding deflazacort for the treatment of DMD on Māori health outcomes. The Committee noted DMD is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. The Committee considered that although there is no evidence to suggest DMD is more prevalent in Māori, this does not exclude the possibility that Māori with DMD experience inequitable access to specialist services and/or inequitable health outcomes.

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

8.3.7. The Committee discussed the impact of funding deflazacort for the treatment of DMD on people who have been underserved by the health system. The Committee did not identify any group with known inequitable health outcomes associated with DMD but noted that the lack of available evidence did not exclude the possible presence of these inequities.

Background

8.3.8. The Committee noted that PTAC previously considered a funding application from a clinician for deflazacort (a product not approved in New Zealand) for people with Duchenne muscular dystrophy (DMD) for whom prednisone is not tolerable, in August 2016. The Committee noted PTAC recommended at the time that the application be declined, and that the available evidence in support of deflazacort as an alternative to prednisone was low quality and did not support a benefit of deflazacort over prednisone in the requested population. The Committee noted that at this time, PTAC requested to review the FOR-DMD randomised controlled trial once it was published.

8.3.9. The Committee noted that in November 2016, the Neurological Subcommittee (now Advisory Committee) reviewed the August 2016 PTAC meeting minutes in relation to deflazacort and considered that in light of new published evidence (Griggs et al. Neurology 2016;87:2123-31), PTAC should review its recommendation; in February 2017, PTAC considered that the Griggs et al. (2016) trial results did not differ in effect from relevant results in a Cochrane review that it had previously considered, and the

Committee's recommendation remained unchanged (that the application for deflazacort for patients with DMD unable to tolerate prednisone be declined).

8.3.10. The Committee noted that in February 2019, PTAC considered correspondence from Muscular Dystrophy New Zealand (MDNZ) requesting that consideration be given to a recently published post hoc analysis of the Ataluren Confirmatory Trial (ACT) DMD study (Shieh et al. Muscle Nerve 2018;58:639-45). The Committee noted PTAC considered the evidence did not change its recommendation for decline but reiterated that it would like to review its recommendation once the FOR-DMD study was published.

Health need

8.3.11. The Committee considered the high health needs of people with DMD and the health needs of their families and whānau were described in the record of the August 2016 PTAC meeting.

8.3.12. The Committee considered the prevalence of DMD in New Zealand likely remains similar to results published from a nationwide, population-based prevalence study of genetic muscle disorders published in 2015 (Theadom et al. Neuroepidemiology. 2019;52:128-35), which reported 104 cases of DMD in New Zealand; a prevalence of 2.45/100,000 people. The Committee considered the study did not show that DMD appeared more common in Māori or Pacific people. However, the Committee did consider that Māori people, disabled people, people who live rurally, and other groups who experience health inequities in New Zealand may experience inequitable access to specialist health services and health outcomes with DMD which were not explored in the study.

8.3.13. The Committee considered that people with DMD experience high unmet health need, due to the disabling nature of the condition, early mortality, and high requirements for care from whānau and health services.

8.3.14. The Committee noted that due to DMD being a genetic disorder, some families and whānau experience higher carer health need from having multiple affected children, which can be particularly challenging.

8.3.15. The Committee reviewed a collection of patient perspectives on deflazacort treatment for DMD submitted by MDNZ. The Committee noted some perspectives reported less-favourable weight gain and reduced behavioural side-effects with deflazacort in comparison to prednisone. The Committee considered the patient perspectives reinforced the consideration that people with DMD in New Zealand and their carers still experience high unmet health needs in spite of currently available treatment options.

8.3.16. The Committee noted the need for effective alternative treatment options for these patients beyond prednisone, including consideration of a potential class effect with corticosteroids.

Health benefit

8.3.17. The Committee reviewed results published from the FOR-DMD trial, a double-blind, parallel-group, randomised clinical trial comparing daily prednisone (n = 65), daily deflazacort (n = 66), and intermittent prednisone (n =66) in boys aged 4 to 7 years with DMD who had not been previously treated with corticosteroids (Guglieri et al. JAMA. 2022;327:1456-68). The Committee noted the composite primary outcome included three end points: 1) rise from the floor velocity; 2) respiratory forced vital capacity (in litres); and 3) participant or parent global satisfaction with treatment measured by the Treatment Satisfaction Questionnaire for Medication. The Committee noted that compared with intermittent prednisone, daily prednisone ($P < 0.001$) and daily deflazacort ($P = 0.017$) were both more effective in terms of the 3-dimensional primary composite outcome, but a statistically significant difference between the 2 daily regimens was not detected ($P = 0.38$). The Committee noted participants in the daily regimen groups experienced better performance than those in the intermittent prednisone regimen group with respect to all secondary motor function outcomes; there were no significant differences between the two daily regimens.

8.3.18. The Committee noted safety outcomes results from the FOR-DMD trial. The Committee noted the between-group difference in weight gain at month 36 was 2.6 kg (98.3% CI, 0.2, 5.0 kg) for daily prednisone vs daily deflazacort ($P = 0.01$). The Committee noted daily deflazacort was associated with greater slowing of growth than daily prednisone; the between-group difference in height at month 36 was 2.3 cm (98.3% CI, 0.7, 3.9 cm) for daily prednisone vs daily deflazacort ($P < 0.001$) in this young age band; impact of this weight gain on later teen years remains unknown. The Committee noted cataracts were reported more frequently in the daily deflazacort group, but none required treatment (2 boys [3%] in the daily prednisone group; 7 boys [10%] in the daily deflazacort group). The Committee noted no treatment group differences were noted for scores on the behavioural rating scales, nor with respect to changes in blood pressure or echocardiographic outcomes. The Committee noted dose reductions occurred in 32 participants (49%) in the daily prednisone group and 23 participants (35%) in the daily deflazacort group, with predominant reasons for reduction being Cushingoid appearance, weight gain, and behavioural changes.

8.3.19. The Committee considered the results from the FOR-DMD trial constituted high-quality evidence indicating no differences in efficacy between the two daily corticosteroid regimens.

8.3.20. The Committee considered safety outcomes and tolerability varied slightly between the two daily regimens, with some favouring prednisone and others favouring deflazacort. The Committee discussed how adverse reactions associated with or intolerance to prednisone is currently managed in clinical practice and considered that the prevailing strategy is likely to involve reducing the prednisone dose (rather than discontinuing treatment entirely) to maintain the child on treatment for as long as the benefits outweigh the risks. This approach aligns with findings from the FOR-DMD trial, where nearly 50% of patients receiving daily prednisone experienced dosage reductions.

8.3.21. The Committee considered the evidence from the FOR-DMD trial indicates that deflazacort is unlikely to provide a substantial additional clinical benefit, including for those patients who experience adverse effects associated with prednisone.

Suitability

8.3.22. The Committee noted the application for deflazacort was for both tablet and oral liquid formulations. The Committee considered the suitability comparable to prednisone/prednisolone, which is currently funded in both tablet and oral liquid forms.

8.3.23. The Committee noted that there is currently no available deflazacort product in New Zealand with Medsafe approval.

Cost and savings

8.3.24. The Committee noted that deflazacort is typically more expensive than prednisone. The Committee considered it unlikely that funding deflazacort would result in cost savings to the health system due to the similar efficacy and safety outcomes associated with both treatments.

Summary for assessment

8.3.25. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for deflazacort if it were to be funded in New Zealand for DMD. This PICO table captures key clinical aspects of the proposal discussed by the Committee.

8.3.26. Due to the Committee's recommendation to decline this application, no economic assessment will be conducted by Pharmac staff at this stage.

Population	Individuals with Duchenne muscular dystrophy who experience significant side effects associated with prednisone treatment.

Intervention	Deflazacort (oral tablets or liquid) as an alternative treatment option. - Dosing recommendations: 0.90 mg/kg once daily (FDA prescribing information – Emflaza. 2017) - Dose may be reduced due to adverse effects associated with treatment (35% according to Guglieri et al. 2022) - Treatment duration is uncertain. Treatment is typically initiated when the child no longer experiences motor progress but before losing muscle strength (~5 years of age), and most children remain on treatment while ambulatory. Duration on treatment once child is non-ambulant will vary based on ongoing risk and benefits of therapy (Birnkrant et al. Lancet Neurol. 2018;17:251-67).
Comparator(s) (NZ context)	Prednisone tablets or prednisolone oral liquid. - Dosing recommendations: 0.75 mg/kg (Birnkrant et al. 2018). - Dose may be reduced due to adverse effects associated with treatment (50% according to Guglieri et al. 2022) - Treatment duration is uncertain, as with deflazacort above.
Outcome(s)	Key therapeutic outcomes of interest (Guglieri et al. 2022): 1. Morbidity measured in terms of a 3-dimensional primary composite outcome (rise from the floor velocity, forced vital capacity (in litres) and participant or parent global satisfaction with treatment): ➢ No statistically significant difference between daily prednisone and daily deflazacort was detected (p = 0.38) 2. Difference in adverse events: ➢ Reduction in weight gain (Between-group difference at month 36 was 2.6 kg (98.3% CI, 0.2 to 5.0 kg) for daily prednisone vs daily deflazacort (P = .01). ➢ Greater slowing of growth (between-group difference in height at month 36 was 2.3 cm (98.3% CI, 0.7 to 3.9 cm) for daily prednisone vs daily deflazacort (P < .001)). ➢ No treatment group differences were noted for scores on the behavioural rating scales, nor with respect to changes in blood pressure or echocardiographic outcomes.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

9. Selexipag - Pulmonary arterial hypertension (PAH), for mono-, dual- and triple combination therapy – new evidence (P-000925, P-000043, P-000681)

Application

9.1. The Committee reviewed the application for selexipag for the mono-, dual- and triple combination therapy for the treatment of pulmonary arterial hypertension (PAH).

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 selexipag for the treatment of pulmonary arterial hypertension be funded with a **high priority** subject to the following Special Authority criteria:

> **Initiation – (PAH monotherapy)** Respiratory specialist, cardiologist, rheumatologist or any relevant practitioner on the recommendation of a respiratory specialist, cardiologist or rheumatologist. Limited to 6 months treatment
> All of the following:
> 1. Patient has pulmonary arterial hypertension (PAH); and

2. PAH is in Group 1, 4 or 5 of the WHO (Venice 2003) clinical classifications; and
3. PAH is in New York Heart Association/World Health Organization (NYHA/WHO) functional class II, III or IV; and
4. Any of the following:
    4.1 All of the following:
        4.1.1 PAH has been confirmed by right heart catheterisation; and
        4.1.2 A mean pulmonary artery pressure (PAPm) greater than 20 mmHg (unless peri Fontan repair); and
        4.1.3 A pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; and
        4.1.4 A pulmonary vascular resistance greater than 2 Wood Units or greater than 160 International Units (dyn s cm−5); and
        4.1.5 Any of the following:
            4.1.5.1 PAH has been demonstrated to be non-responsive in vasoreactivity assessment using iloprost or nitric oxide, as defined in the 2022 ECS/ERS Guidelines for PAH; or
            4.1.5.2 Patient has not experienced an acceptable response to calcium antagonist treatment, according to a validated risk stratification tool**; or
            4.1.5.3 Patient has PAH other than idiopathic / heritable or drug-associated type; or
    4.2 Patient is a child with PAH secondary to congenital heart disease or PAH due to idiopathic, congenital or developmental lung disorders including severe chronic neonatal lung disease; or
    4.3 Patient has palliated single ventricle congenital heart disease and elevated pulmonary pressures or a major complication of the Fontan circulation requiring the minimising of pulmonary/venous filling pressures; and
5. Both:
    5.1 Selexipag is to be used as PAH monotherapy; and
    5.2 Either:
        5.2.1 Patient has experienced intolerable side effects on sildenafil and both the funded endothelin receptor antagonists (i.e. both bosentan and ambrisentan); or
        5.2.2 Patient has an absolute contraindication to sildenafil and an absolute or relative contraindication to endothelin receptor antagonists.

Initiation – (PAH dual therapy) Respiratory specialist, cardiologist, rheumatologist or any relevant practitioner on the recommendation of a respiratory specialist, cardiologist or rheumatologist. Limited to 6 months treatment
All of the following:
1. Patient has pulmonary arterial hypertension (PAH); and
2. PAH is in Group 1, 4 or 5 of the WHO (Venice 2003) clinical classifications; and
3. PAH is in New York Heart Association/World Health Organization (NYHA/WHO) functional class II, III or IV; and
4. Any of the following:
    4.1 All of the following:
        4.1.1 PAH has been confirmed by right heart catheterisation; and
        4.1.2 A mean pulmonary artery pressure (PAPm) greater than 20 mmHg (unless peri Fontan repair); and
        4.1.3 A pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; and
        4.1.4 A pulmonary vascular resistance greater than 2 Wood Units or greater than 160 International Units (dyn scm−5); and
        4.1.5 Any of the following:
            4.1.5.1 PAH has been demonstrated to be non-responsive in vasoreactivity assessment using iloprost or nitric oxide, as defined in the 2022 ECS/ERS Guidelines for PAH (see note below for link to these guidelines) † ; or
            4.1.5.2 Patient has not experienced an acceptable response to calcium antagonist treatment, according to a validated risk stratification tool**; or
    4.2 Patient has PAH other than idiopathic / heritable or drug-associated type; or
    4.3 Patient is a child with PAH secondary to congenital heart disease or PAH due to idiopathic, congenital or developmental lung disorders including severe chronic neonatal lung disease; or
    4.4 Patient has palliated single ventricle congenital heart disease and elevated pulmonary pressures or a major complication of the Fontan circulation requiring the minimising of pulmonary/venous filling pressures; and
5. All of the following:
    5.1 Selexipag is to be used as PAH dual therapy with either sildenafil or an endothelin receptor antagonist; and
    5.2 Either:
        5.2.1 Patient has an absolute contraindication to or has experienced intolerable side effects on sildenafil; or
        5.2.2 Patient has an absolute or relative contraindication to or experienced intolerable side effects with both funded endothelin receptor antagonists; and
    5.3 Either:

5.3.1 Patient has tried a PAH monotherapy for at least three months and remains in an unacceptable risk category according to a validated risk stratification tool**; or
5.3.2 Patient is presenting in NYHA/WHO functional class III or IV, and in the opinion of the treating clinician would benefit from initial dual therapy

Initiation – (PAH triple therapy) Respiratory specialist, cardiologist, rheumatologist or any relevant practitioner on the recommendation of a respiratory specialist, cardiologist or rheumatologist. Limited to 6 months treatment
All of the following:
1. Patient has pulmonary arterial hypertension (PAH); and
2. PAH is in Group 1, 4 or 5 of the WHO (Venice 2003) clinical classifications; and
3. PAH is in New York Heart Association/World Health Organization (NYHA/WHO) functional class II, III or IV; and
4. Any of the following:
   4.1 All of the following:
      4.1.1 PAH has been confirmed by right heart catheterisation; and
      4.1.2 A mean pulmonary artery pressure (PAPm) greater than 20 mmHg (unless peri Fontan repair); and
      4.1.3 A pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; and
      4.1.4 A pulmonary vascular resistance greater than 2 Wood Units or greater than 160 International Units (dyn scm−5); and
      4.1.5 Any of the following:
         4.1.5.1 PAH has been demonstrated to be non-responsive in vasoreactivity assessment using iloprost or nitric oxide, as defined in the 2022 ECS/ERS Guidelines for PAH † ; or
         4.1.5.2 Patient has not experienced an acceptable response to calcium antagonist treatment, according to a validated risk stratification tool**; or
         4.1.5.3 Patient has PAH other than idiopathic / heritable or drug-associated type; or
   4.2 Patient is a child with PAH secondary to congenital heart disease or PAH due to idiopathic, congenital or developmental lung disorders including severe chronic neonatal lung disease; or
   4.3 Patient has palliated single ventricle congenital heart disease and elevated pulmonary pressures or a major complication of the Fontan circulation requiring the minimising of pulmonary/venous filling pressures; and
5. Both:
   5.1 Selexipag is to be used as PAH triple therapy; and
   5.2 Any of the following:
      5.2.1 Patient is on the lung transplant list; or
      5.2.2 Patient is presenting in NYHA/WHO functional class IV; or
      5.2.3 Both:
         5.2.3.1 Patient has tried PAH dual therapy for at least three months and has not experienced an acceptable response to treatment according to a validated risk stratification tool**; and
         5.2.3.2 Patient does not have major life-threatening comorbidities and triple therapy is not being used in a palliative scenario.

Continuation
Respiratory specialist, cardiologist, rheumatologist or any relevant practitioner on the recommendation of a respiratory specialist, cardiologist or rheumatologist. Re-assessment required after 2 years.

Patient is continuing to derive benefit from selexipag treatment according to a validated PAH risk stratification tool.

Notes: † The European Respiratory Journal Guidelines can be found here: 2022 ECS/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension PAH ** the requirement to use a validated risk stratification tool to determine insufficient response applies to adults. Determining insufficient response in children does not require use of a validated PAH risk stratification tool, where currently no such validated tools exist for PAH risk stratification in children.

9.4. The Committee recommended based on the following:

- The high unmet health need
- The increased suitability of an oral tablet in comparison to currently funded inhaled treatments
- The savings to the health sector from reduced hospitalisations and disease progression

Discussion

Māori impact

9.5. The Committee discussed the impact of funding selexipag for the treatment of PAH on Māori health areas of focus and Māori health outcomes. The Committee considered anecdotal evidence that Māori may present with PAH at a younger age, than other population groups in New Zealand. The Committee also considered that access to current treatments might be reduced due to the need to relocate closer to large hospitals.

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

9.6. The Committee noted several studies that reported low socioeconomic status (SES) was associated with worse disease, and a higher risk of clinical worsening and mortality for individuals with idiopathic PAH *(*Talwar et al. Pulm Circ. 2016;6:191-5*;* Wu et al. Am J Respir Crit Care Med. 2013;187:303-10).

9.7. The Committee further considered that access to current treatments may be inequitable, including for those people in rural areas unable access an emergency care centre, considered necessary for parenteral epoprostenol use due to potential intravenous line infections with sepsis. In addition, Iloprost relies on the use of nebulisers for inhalation, and whilst a number of nebulisers are provided by the hospital service, subsequent ones must be funded by the individual, providing a barrier to access for those who cannot afford these.

Background

9.8. The Committee noted treatments for PAH had been extensively considered previously by the PAH Subcommittee and subsequent PAH panel, and consultation feedback on PAH treatment was received in 2023. The Committee noted it had previously considered the use of selexipag in May 2016 and recommended the treatment with a low priority. The Committee noted a new consumer application was received that has provided updated clinical benefit information.

Health need

9.9. The Committee noted it had previously considered the health need of those with PAH in May 2016.

9.10. The Committee noted that PAH is a chronic disease of the pulmonary vasculature leading to significant morbidity and mortality, and while new therapeutics have improved symptom control, PAH remains a disease without a cure with a median survival of 5 to 7 years (Mathai et al. Ann Am Thorac Soc. 2016;13:31-9).

9.11. The Committee noted PAH is classified as group 1 of the World Health Organization (WHO) pulmonary hypertension classification subgroups, which includes various causes of PAH including idiopathic, familial, connective tissue disorders, shunts, HIV, drugs, toxins veno-capillary and newborn disease (2022 ESC/ERS Guidelines).

9.12. The Committee noted a study of 55 people with PAH (groups I-IV ineligible for angioplasty/endarterectomy) reported that the Physical Component Summary (PCS) and the Mental Component Summary (MCS) measures of health related quality of life (HRQoL) were poor (PCS=37.13, 8.18 standard deviation (SD); MCS=42.42, SD 10.88) but stable over 3 years of follow-up (Halimi et al. ERJ Open Res. 2021;7:00617-2020). In addition an 18 month study performed of 185 people with PAH reported at baseline, individuals had significant impairment of HRQoL, with anxiety, depression, dyspnoea and severe fatigue(Yorke et al. BMJ Open Respir Res. 2018;5:e000263).

9.13. The Committee noted a survey conducted by the European Pulmonary Hypertension Association of 455 individuals and carers in five countries. Over half reported that pulmonary hypertension had a significant impact on daily life: for example, taking part in exercise or sport, climbing stairs and performing everyday tasks such as housework or food shopping (Yorke et al. BMJ Open Respir Res. 2018;5:e000263).

9.14. The Committee noted a study that reported when living with a person with PAH, caregivers (57%) found it to be a physically draining and it disrupted their other daily activities, whilst nearly half of caregivers surveyed felt they were exhausted because of the additional demands from the person (Verma et al J Exerc Rehabil. 2016;12:386-92).

9.15. The Committee considered whilst the prevalence of PAH in New Zealand is not well documented, UK prevalence estimates of 50 cases per million suggest approximately 250 people in New Zealand have PAH. The Committee considered the UK data would be relevant to the New Zealand population.

9.16. The Committee considered anecdotally that, while there is a lack of evidence to suggest Māori are more likely to suffer from PAH than other ethnic groups (noting small numbers), Māori may present with PAH at a younger age than other population groups in New Zealand. The Committee also considered that access to current treatments might be reduced due to the need to relocate closer to large hospitals.

9.17. The Committee noted several studies that reported that low socioeconomic status (SES) was associated with worse disease at initial presentation, and a higher risk of clinical worsening and mortality for individuals with idiopathic PAH (Talwar et al. Pulm Circ. 2016 ; Wu et al. Am J Respir Crit Care Med. 2013).

9.18. The Committee noted that approximately 10% of cases of PAH are drug induced (Hlavaty et al. Br J Clin Pharmacol. 2022;88:5227-37), with a variety of compounds associated with the onset of PAH. The Committee considered that methamphetamine use is one compound that contributes to developing PAH in the New Zealand context.

9.19. The Committee noted the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.

Health benefit

Monotherapy

9.20. The Committee noted Galiè et al. Adv Ther.2022;39:796-810 reported the outcomes of the GRIPHON multicentre, double-blind, randomised, placebo-controlled event-driven phase 3 study and open label extension (OLE). The trial reported the following outcomes at 7 years of treatment:

- Kaplan–Meier survival estimates at 1, 3, 5 and 7 years in individuals randomised to selexipag in GRIPHON (n = 574) were 92.0%, 79.3%, 71.2% and 63.0%, respectively.
- There were 80.5% people treated with a stable dose of an endothelin receptor antagonist (ERA) and/or a phosphodiesterase 5 inhibitor (PDE5)i: 31.2% with both an ERA and a PDE5i, 16.4% with an ERA, and 32.9% with a PDE5i.
- There were 163 (28.4%) people initiated a new class of PAH therapy. The most common were an ERA (n = 40; 7.0%), a PDE5i (n = 42; 7.3%) and prostacyclin or its analogue (n = 55; 9.6%). However, 86.3% of the selexipag exposure in the survival analysis set (n = 574) was accumulated without or prior to the addition of any new PAH therapies.

9.21. The Committee noted the Marques et al. Eur. Heart J. 2022;43(Suppl 2);ehac544.1932 conference abstract reported outcomes of the RAMPHA multicentre, observational and retrospective cohort study. The abstract reported the following outcomes:

- Of 29 people, 11 (38%) experienced improved functional class, and one individual experienced disease progression (p=0.001).
- Three experienced improved risk-profile in the exercise test and, in the remaining individuals, a quantitative improvement was reported.
- N-terminal pro b-type natriuretic peptide (NT-proBNP) levels were not significantly better (924ng/l IQR 1209 vs 760ng/l IQR 1397).

- There were not changes in right ventricular function in the echocardiographic parameters.
- There were 86% of people who experienced adverse effects, but there were no discontinuations. The most common side effect was headache.
- The titration lasted 68 days (IQR 72) and 38% of the individuals had the maximum dose.

9.22. The Committee noted Chin et al. J Am Coll Cardiol .2021;78:1393-1403 reported the outcomes of the Triton multicentre, double-blind, randomised phase 3b study that evaluated the health benefit of initial triple (macitentan, tadalafil and selexipag) versus initial double (macitentan, tadalafil and placebo) therapy. The trial reported the following outcomes:

- At week 26, both groups had reduced pulmonary vascular resistance compared with baseline (by 54% and 52%), with no significant difference between groups (ratio of geometric means: 0.96; 95% confidence interval: 0.86, 1.07; P = 0.42).
- Six-minute walk distance and NT-proBNP improved by week 26, with no difference between groups.
- Risk for disease progression (to end of main observation period) was reduced with initial triple versus initial double therapy (hazard ratio: 0.59; 95% confidence interval: 0.32, 1.09).

9.23. The Committee also noted the following studies:

- Coghlan et al. ERJ Open Res. 2023;9:00456-2022
- McLaughlin et al. J Heart Lung Transplant. 2024;43:272-83.
- Rosenkranz et al. Eur J Heart Fail. 2022;24:205-14.
- Qin et al. Curr Probl Cardiol. 2023;48:101466.
- Chen et al. Pulm Pharmacol Ther. 2022:72:102100
- Wang et al. Drug Deliv. 2018;25:1898-1909
- Gaine et al. Chest. 2021;160:277-86

9.24. The Committee noted the Coghlan et al. Am J Cardiovasc Drugs. 2018;18:37-47 post hoc subgroup analysis of selexipag triple therapy in GRIPHON reported treatment with selexipag was associated with delayed disease progression, whilst the Tsang et al. Clin Respir J. 2023;17:1209-22 retrospective cohort study reported that selexipag initiation within 12 months of PAH diagnosis was associated with reductions in all-cause hospitalisation but not PAH-related hospitalisation, compared with not initiating prostacyclin agonists within 12 months. The Committee considered that treatment with selexipag might reduce time spent for the individual in hospital, and delay time to disease progression and further treatment.

9.25. The Committee considered there was a lack of head-to-head comparison studies with other prostacyclin agonists and due to the rarity of the condition, there were a limited number of studies of each agent, with most being small in size.

9.26. The Committee considered that there was a lack of evidence to confirm whether there would be significant differences in mortality rates between people receiving selexipag compared to inhaled iloprost.

9.27. The Committee considered an improvement in the six-minute walk test is a clinically meaningful outcome though its implications for health-related quality of life and final clinical endpoints was uncertain.

9.28. The Committee considered there were clinical improvements irrespective of baseline severity and treatment (mono-, dual-, triple-) and dose tolerated.

Suitability

9.29. The Committee considered the use of selexipag would result in a substantial reduction in administration frequency compared to iloprost which must be inhaled between 6 to 9 times a day through a nebuliser, over the course of 4 to 10 minutes per session. The Committee considered this might improve adherence to treatment and therapeutic benefit. The Committee considered selexipag, compared with inhaled iloprost, might have a more consistent therapeutic effect over the course of a day due to the short half-life of inhaled iloprost compared to selexipag, as well as increased adherence to selexipag as a twice daily oral administration

9.30. The Committee considered the currently funded prostacyclin agonists including iloprost and epoprostenol were relatively unsuitable. Iloprost must be nebulised 6-9 times per day, with treatment sessions ranging from 4-10 minutes each. The Committee noted anecdotal evidence this may be up to 30 minutes for some individuals. The Committee considered due to the increased burden of administering the treatment, it may result in reduced use. In addition, the Committee noted epoprostenol, which is predominantly used as a bridge to a lung transplant or in emergency situations, has a risk of infection due to the need for continuous infusion.

9.31. The Committee was made aware of a survey study which reported that there was a decrement in health-related quality of life (a disutility), as measured by the EQ-5D-5L UK tariff, associated with inhaled prostacyclin agonists compared to oral agents (Davies et al. Patient Preference Adherence. 2018;12:1079-88). The Committee considered that such a disutility was likely to apply for 30 minutes with each administration of the inhaled agent, and this was an appropriate parameter to include in future economic modelling of selexipag.

9.32. The Committee considered some of the current treatments may have inequitable access including for individuals in rural areas that may be unable access an emergency care centre, considered necessary for parenteral epoprostenol use due to potential intravenous line infections with sepsis. In addition, Iloprost relies on the use of nebulisers for inhalation. Although a number of nebulisers are provided by the hospital service, subsequent ones must be funded by the individual, providing a barrier to access for those who cannot afford these.

9.33. The Committee considered anecdotal evidence that the use of epoprostenol required people to relocate to be closer to larger hospitals due to the infection risk.

Cost and savings

9.34. The Committee considered that the majority of individuals would not be titrated to the maximum dose of selexipag. The Committee noted 38% of participants received the maximum dose in the RAMPHA study. The Committee further notes that in the GRIPHON study, 23% received the lowest dose (200-400 micrograms twice daily [bid]), 31% received the medium dose (600-1000 micrograms [bid)] and 43% received the high dose (1200-1600 micrograms [bid]). The Committee considered that similar dosing patterns would be observed in New Zealand if selexipag were to be funded.

9.35. The Committee considered that the costs associated with physician visits for treatment initiation and drug titration would be similar between selexipag and iloprost.

9.36. The Committee noted an observational database study which reported that selexipag was associated with a lower rate of hospitalisation (RR 0.40 [95% CI 0.22, 0.75) and outpatient visits (RR 0.26 [95% CI 0.17, 0.39]) compared to inhaled iloprost (Song et al. J Health Econ Outcomes Res. 2022;9:151-160).

9.37. The Committee considered if selexipag were to be funded as a first-line prostacyclin inhibitor, most people would transition from iloprost to selexipag given its suitability advantage. The Committee considered that selexipag was unlikely to displace use of epoprostenol because of the end-stage setting in which epoprostenol is used.

9.38. The Committee considered infections due to epoprostenol treatment would require hospitalisation, treatment, and replacement intravenous access. The Committee

considered many centres now used specialist dressings to help mitigate infection, however these were expensive. The Committee noted Camara et al Int J Mol Sci. 2023; 24: 6434 a multicentre retrospective study between 2004-2019 reported blood stream infections from iloprost when given intravenously (this presentation is not funded in New Zealand) and epoprostenol of approximately 4.3% and 76.9% respectively.

Funding criteria

9.39. The Committee considered selexipag would be appropriate as a monotherapy for individuals who are intolerant to other therapies.

Summary for assessment

9.40. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for selexipag if it were to be funded in New Zealand for PAH. 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 pulmonary arterial hypertension who require treatment with a prostacyclin receptor agonist as part of monotherapy or dual therapy or triple therapy regimen
Intervention	Selexipag tablets • Up to 1600 mg twice per day (Medsafe Data Sheet – Selexipag [UPTRAVI]) In combination with other PAH medications, primarily endothelin receptor agonists (ERAs [ambrisentan, bosentan]) and phosphadiesterase Type 5 inhibitors (PDE5is [sildenafil, tadalafil]) • GRIPHON reported that 23% of participants received the lowest maintenance dose (200-400 micrograms twice daily [bid]), 31% received the medium dose (600-1000 micrograms [bid)] and 43% received the high dose (1200-1600 micrograms [bid]) (Galiè et al. Adv Ther.2022;39:796-810)
Comparator(s) (NZ context)	Iloprost solution for inhalation • At a dose of 5 mcg, inhaled up to nine times per day (Medsafe Data Sheet – Iloprost [VEBULIS]) In combination with other PAH medications
Outcome(s)	Improved health-related quality of life • Avoidance of a disutility associated with inhaled prostacyclin agonists (i.e., iloprost) compared to oral agents (Davies et al. Patient Preference Adherence. 2018;12: 1079-1088). • This disutility would apply for 30 minutes for each administration of the inhaled agent. Potential reduction in rate of hospitalisation and outpatient visits • An observational database study reported that selexipag was associated with a lower rate of hospitalisation (RR 0.40 [95% CI 0,.22, 0,.75) and outpatient visits (RR 0.26 [95% CI 0.17, 0.39]) compared to inhaled iloprost (Song et al. J Health Econ Outcomes Res. 2022;9:151-160).
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.	

10. Macitentan for pulmonary arterial hypertension (P-000889)

Application

10.1. The Committee reviewed the application for macitentan for the treatment of pulmonary arterial hypertension (PAH) from the supplier, and the supporting applications from the Thoracic Society of Australia and New Zealand (TSANZ) and the Health NZ | Te Whatu Ora Te Toka Tumai Auckland Pulmonary Vascular Disease Clinic. In addition, the Committee noted a letter from PAH Physicians Aotearoa who requested funding for macitentan as an alternative to bosentan and ambrisentan.

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 macitentan for the treatment of pulmonary arterial hypertension be **declined**.

10.3.1. The Committee made this recommendation based on the substantially higher cost of macitentan compared to existing funded treatments, but considered that in respect to treating pulmonary arterial hypertension there is a class-effect for endothelin receptor antagonists (ERAs), and macitentan could still be considered in future commercial activities.

10.4. The Committee recommended the Cardiovascular Advisory Committee review the proposed Special Authority Criteria for macitentan for PAH.

10.5. The Committee **recommended** that macitentan for the treatment of portopulmonary hypertension be funded with **low priority.**

10.6. The Committee made this recommendation based on:

- The high health need of the population
- The short duration of treatment given its use as a bridge to transplant
- The evidence demonstrating an improvement in pulmonary vascular resistance
- Lack of head-to-head evidence for the currently funded treatment.
- The substantially higher cost of macitentan compared to the existing funded treatments.

10.7. The Committee recommended the Cardiovascular Advisory Committee and the Gastrointestinal Advisory Committee advise Pharmac on Special Authority criteria for macitentan for portopulmonary hypertension.

Discussion

Māori impact

10.8. The Committee discussed the impact of funding of macitentan for the treatment of PAH on Māori health areas of focus and Māori health outcomes. The Committee considered anecdotal evidence that Māori may present with PAH at younger ages than other population groups in New Zealand. The Committee also considered that access to current treatments might be reduced due to the need to relocate closer to large hospitals. than other population groups in New Zealand.

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

10.9. The Committee noted several studies that reported that experiencing low socioeconomic status (SES) was associated with worse disease, and a higher risk of clinical worsening and mortality for individuals with idiopathic PAH *(*Talwar et al. Pulm Circ. 2016;6:191-5*;* Wu et al. Am J Respir Crit Care Med. 2013;187:303-10).

Background

10.10. The Committee noted macitentan is currently listed on the Pharmac Options for Investment list for the treatment of PAH. The application was assessed by PTAC in May 2015, who recommended macitentan be funded with a low priority for the treatment of PAH.

10.11. The Committee noted the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension, which recommend the use of:

- Initial combination therapy (ERA + phosphodiesterase 5 inhibitor) over monotherapy (ERA or phosphodiesterase 5 inhibitor) for people with PAH and low or intermediate risk (Class I level B)
- Initial combination therapy with ambrisentan or macitentan with tadalafil (Class I level B)

- Sequential drug combination therapy of macitentan following a PDE5i/prostacyclin to reduce morbidity/mortality events (Class I level B).

Health need

10.12. The Committee noted their discussion of the health need of people with PAH when considering the funding application for selexipag during this meeting.

10.13. The Committee noted the 2022 ESC/ERS PAH guidelines reported that there is evidence for initial combination therapy use of ambrisentan or macitentan with tadalafil. The Committee noted ambrisentan is currently funded for Groups 1, 4 and 5 PAH as third-line monotherapy, in second-line dual therapy or in triple therapy.

10.14. The Committee considered there would an increased health need in those people experiencing refractory disease or who have experienced adverse effects on current treatments.

10.15. The Committee noted portopulmonary hypertension, a subset of PAH (2022 ESC/ERS PAH guidelines, sections 4.1 and 7.4), is a rare, severe complication of chronic liver disease. It can be rapidly progressive and advance to a point where it precludes liver transplantation. Members considered the number of patients with portopulmonary hypertension in New Zealand to be very small, and PAH treatments are often used as a bridge to transplant. Members noted the use of funded bosentan can be limited by abnormalities in liver function tests. Health need is high in this condition.

Health benefit

10.16. The Committee noted the SERAPHIN trial, which was an considered by PTAC in May 2015 (Pulido et al. N Engl J Med.2013;369:809-18). The Committee noted that since their discussion of the SERAPHIN trial analyses of data from that trial had been published including:

- Galie et al. Eur Heart J. 2017;38:1147-1155 on the effect of macitentan on haemodynamic parameters and NT-proBNP levels
- Souza et al. PLoS One.2018;13:e0193226 on the association between the six-minute walk distance and long-term outcomes
- Mehta et al. Chest. 2017;151:106-18 on the effect of macitentan on health related quality of life
- Krause et al. Pulm Pharmacol Ther. 2018:49:140-6 modelling pharmacokinetic, efficacy and haemodynamic effects
- McLaughlin et al. J Am Coll Cardiol. 2018 ;71:752-63 on the impact of morbid events on the risk of subsequent mortality.

10.17. The Committee noted a further analysis, Souza et al. Adv Ther. 2022;39:4374-90, reported the results of the open-label extension phase of SERAPHIN.

- In the long-term safety set, Kaplan-Meier survival estimates (95% CI) at 1, 3, 5, 7 and 9 years were 95.0% (91.3, 97.1), 84.0% (78.6, 88.2), 73.3% (66.6, 78.9), 62.6% (54.6, 69.6) and 52.7% (43.6, 61.0), respectively.
- There was a loss of people to follow up as people switched to commercially available macitentan.
- Safety reporting did not include the initial SERAPHIN study, and the Committee considered that people unable to tolerate macitentan may have been excluded in the extension study.
- In the open label and long-term safety sets more than 95% of people experienced at least one adverse event, with over 64% experiencing a serious adverse event.
- Peripheral oedema occurred in 26% of long-term safety set patients measured.

- Abnormalities in liver function were observed in people receiving macitentan; the Committee considered that physicians would need to monitor liver function.

10.18. The Committee noted the PORTICO trial, a phase four, multicentre randomised control trial in which 85 people with portopulmonary hypertension were randomised to 10 mg macitentan or placebo for 12 weeks, followed by a 12 week open-label extension (Sitbon et al. Lancet Respir Med. 2019;7:594-604).

10.18.1. At week 12, the geometric mean ratio of baseline pulmonary vascular resistance was 0.63 (95% CI 0.58, 0.67) in the macitentan group and 0.98 (95% CI 0.91, 1.05) in the placebo group (95% CI 0.59, 0.72; p<0.01), corresponding to a 35% (95% CI 28, 41) reduction in pulmonary vascular resistance with macitentan versus placebo.

10.18.2. The Committee noted nominal improvements in the six-minute walk test (6MWT) in individuals initially treated with macitentan were maintained in the weeks 1-12 of the open label phase.

- Individuals who switched to receive macitentan in the weeks 13-24 open label treatment period did experience some improvement in 6MWT, however the Committee considered this may reflect a placebo effect or an effect from monitoring and increased healthcare access ('Hawthorne effect'), as some increase in 6MWT was observed prior to starting the open label extension macitentan.
- Further, Members considered the nominal improvements in 6MWT in the trial were limited by:
    - the 6MWT results did not reach statistical significance (+6.4 metres (m) change from baseline to week 12 for macitentan, -2.4 m for placebo, difference in changes +9.7m (95% CI -14.5, +34.0m; p=0.43);
    - the 6MWT test was a secondary not the primary endpoint; and
    - as the statistical methods did not correct for multiple testing in the analyses of the secondary endpoints, the study regarded all secondary endpoint analyses (6MWT included) as merely exploratory.

10.18.3. The Committee considered the adverse events and serious adverse events to be comparable between the macitentan and placebo arms. Peripheral oedema was the most common adverse effect when receiving macitentan.

10.18.4. The Committee noted the study was small, but considered this was due to the rarity of the condition.

10.19. The Committee noted the MAESTRO trial, which was a phase three, multicentre, double-blind, randomised trial where 226 people with Eisenmenger syndrome were randomised to 10mg macitentan or placebo for 16 weeks (Gatzoulis et al. Circulation. 2019;139:51-63).

10.19.1. In the macitentan group the 6MWT walking distance did not improve compared to baseline (18.3 mean increase, 84.4 m standard deviation (SD)) when compared with the change for placebo (19.7, SD 53.0 m; least-square mean difference between macitentan and placebo -4.7 m; 95% CI -22.8,13.5; p=0.61).

10.19.2. The Committee noted a small subgroup underwent a specialised haemodynamic substudy that did report an improvement in pulmonary vascular resistance when treated with macitentan compared with placebo. The Committee noted the authors of the study concluded there were no compelling evidence for macitentan over placebo in the treatment of Eisenmenger syndrome.

10.20. The Committee noted the REPAIR trial, was a phase four, multicentred, open-label trial in which 42 people received 10mg macitentan with or without a phosphodiesterase-5 inhibitor for 52 weeks (Noordegraaf et al. JACC Cardiovasc Imaging. 2022;15:240-53).

10.20.1. The Committee noted this study compared the effect of macitentan between those people with PAH with no prior treatment, those with no prior treatment in combination with a PDE5I, and those on stable background PDE5i treatment.

10.20.2. At week 26, right ventricular stroke volume increased by 12 ml (96% CI 8.4,15.6 ml; $p < 0.01$) and pulmonary vascular resistance decreased by 38% (99% CI 31%, 44%; $p < 0.01$).

10.20.3. The Committee noted the study population was small.

10.21. The Committee noted the TRITON trial, which was a phase 3b, double-blinded randomised study where 247 people with PAH and who were treatment-naïve received double (macitentan, tadalafil and placebo) or triple (macitentan, tadalafil and selexipag) therapy for 26 weeks (Chin et al. J Am Coll Cardiol. 2021;78:1393-403).

10.21.1. At 26 weeks, no differences in pulmonary vascular resistance or exploratory analyses (6MWT and NT-proBNP) were observed.

10.21.2. The Committee considered there was no reported difference in health benefit between triple and dual therapy.

10.22. The Committee noted the Benza et al. Pulm. Circ. 2020;10 retrospective cohort study of 6452 people with PAH receiving ERAs, which reported an 18% lower adjusted mortality risk with macitentan compared with ambrisentan (hazard ratio (HR) 0.82; 95% CI 0.72, 0.93; $p < 0.01$), and a 39% lower risk than bosentan (HR 0.61; 95% CI 0.53, 0.71; $p < 0.01$). Ambrisentan was associated with a 26% lower mortality risk than bosentan (HR 0.74; 95% CI 0.67, 0.83; $p < 0.01$).

10.23. The Committee noted the Lau et al. J Med Econ. 2024;27:1-11 retrospective cohort study of 436 people assessing adherence of bosentan, ambrisentan and macitentan proxied by a person receiving ≥80% of doses over 12-months (medicine persistence).

10.23.1. The Committee noted persistence was highest in macitentan (65.3%) compared with bosentan (58.0%).and ambrisentan (56.5%)

10.23.2. The Committee considered this increase in adherence may be due to reduced oedema.

10.24. The Committee noted the Duo-Ji & Long. Int J Cardiol. 2017:234:90-8 indirect comparison network metanalysis of 10 studies including 2172 people. The Committee noted the authors considered ambrisentan the most appropriate therapy amongst four ERAs (macitentan, ambrisentan, bosentan and sitaxsentan). The Committee noted macitentan was not associated with the same health benefit in the 6MWT or clinical worsening reductions compared with the other ERAs in the study.

10.25. The Committee noted the following studies:

10.25.1. Ghofrani et al. Lancet Respir Med. 2017;5:785-94

10.25.2. Wei et al. J Am Heart Assoc. 2016;5:e003896

10.25.3. Aldalaan et al. Pulm Circ. 2022;12:e12083.

10.25.4. Aypar et al. Cardiol Young. 2018;28:542-7.

10.25.5. Aypar et al. Cardiol Young.2020;30:681-5.

10.25.6. Safdar et al. South Med J. 2017;110:223-8

10.25.7. Blok et al. Int J Cardiol.2017:227:51-2

10.25.8. Li et al. Front Cardiovasc Med. 2022:9:977110

10.26. The Committee considered macitentan to have comparable health benefit to bosentan and ambrisentan for the treatment of PAH. The Committee considered the studies varied

in design, with few head-to-head comparator studies. The Committee considered macitentan may be better tolerated and have improved adherence compared to other ERAs.

10.27. The Committee considered that given the PORTICO trial results (albeit it was a small study with no functional differences in 6MWT) and the absence of an equivalent randomised control trial with bosentan, there was more evidence for the efficacy of macitentan for the treatment of portopulmonary hypertension. Moreover, the frequent liver function abnormalities associated with bosentan, with less frequent associated liver function abnormalities reported with macitentan, meant that macitentan would be considered the preferred ERA for portopulmonary hypertension.

10.28. The Committee considered there to be a class-effect regarding the health benefit of ERAs.

10.29. The Committee noted macitentan is associated with oedema and liver metabolite abnormalities.

Suitability

10.30. The Committee noted that like ambrisentan, macitentan is an oral agent that is administered once daily, which is less of a pill burden compared with bosentan which is administered orally twice a day. The Committee considered this difference small.

10.31. The Committee noted that macitentan has a reduced number of drug-drug interactions compared to other ERAs. Macitentan interacts only with rifampicin, and these two medicines are not frequently used together.

Cost and savings

10.32. The Committee considered macitentan would not create any significant increase in health sector expenditure aside from direct treatment costs.

10.33. The Committee considered the treatment was more expensive than current ERAs but did not show an increase in health benefit.

10.34. The Committee considered bosentan would not be used for the treatment of portopulmonary hypertension and would not be a comparator for macitentan. The Committee considered ambrisentan would be the appropriate comparator for this population.

Funding criteria

10.35. The Committee considered macitentan for portopulmonary hypertension should not be restricted to use in adults.

Summary for assessment

10.36. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for macitentan if it were to be funded in New Zealand for the treatment of PAH. 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 pulmonary arterial hypertension who require treatment with an endothelin receptor antagonist part of a monotherapy, dual therapy or triple therapy regimen.	
Intervention	Macitentan tablets • Dose of 10mg once daily (Medsafe Data Sheet – Macitentan [Opsumit]) In combination with other PAH medications, primarily prostacyclin receptor agonists (PRAs [iloprost, epoprostenol]) and phosphadiesterase Type 5 inhibitors (PDE5is [sildenafil, tadalafil])	
Comparator(s) (NZ context)	Bosentan tablets • Initial dose of 62.5mg twice daily, increasing to a maintenance dose of 125mg twice daily after four weeks (Medsafe Data Sheet – Bosentan [BOSENTAN DR REDDY'S]) in combination with other PAH medications	Ambrisentan tablets • At an initial dose of 5mg once daily, increasing to a once daily dose of 10mg for some individuals (Medsafe Data Sheet – Ambrisentan [AMBRISENTAN VIATRIS]) in combination with other PAH medications
Outcome(s)	There is a lack of evidence that macitentan offers a health benefit beyond that of other endothelin receptor agonists as an add-on therapy for the treatment of PAH.	
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		

10.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for macitentan if it were to be funded in New Zealand for the treatment of portopulmonary hypertension. 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 portopulmonary arterial hypertension who require treatment with an endothelin receptor antagonist as monotherapy or part of a dual therapy or triple therapy regimen.
Intervention	Macitentan tablets • dose of 10mg once daily (Medsafe Data Sheet – Macitentan [Opsumit]) in combination with other PAH medications, primarily prostacyclin receptor agonists (PRAs [iloprost, epoprostenol]) and phosphadiesterase Type 5 inhibitors (PDE5is [sildenafil, tadalafil])
Comparator(s)	Ambrisentan tablets • at an initial dose of 5mg once daily, increasing to a once daily dose of 10mg for some individuals (Medsafe Data Sheet – Ambrisentan [AMBRISENTAN VIATRIS]) in combination with other PAH medications
Outcome(s)	Macitentan is associated with a health benefit relative to placebo (Sitbon et al. Lancet Respir Med. 2019;7:594-604).
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Pembrolizumab for 1L treatment of persistent, recurrent or metastatic cervical cancer in addition to chemotherapy, for patients with a PD-L1 combined positive score of 1 or more (P-001954)

Application

11.1. The Committee reviewed the application for pembrolizumab in addition to chemotherapy, with or without bevacizumab in the treatment of persistent, recurrent, or metastatic cervical cancer.

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 pembrolizumab in addition to chemotherapy **with** bevacizumab for the treatment of persistent, recurrent or metastatic cervical cancer be **declined**.

11.4. The Committee recommended based on the following:

- Insufficient evidence of additional health benefits when combined with bevacizumab, compared to pembrolizumab alone.
- Adverse effects associated with bevacizumab including fistulae formation
- The clinical trial design was not powered to assess bevacizumab benefit, with results that had wide over lapping confidence intervals.

11.5. The Committee **recommended** that pembrolizumab in addition to chemotherapy, **without** bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer be funded with **high priority**.

> **Initial application – (cervical cancer, metastatic, recurrent, persistent),** only from any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has persistent, metastatic or recurrent cervical cancer
> 2. The cancer is not suitable for curative treatment with either surgical resection or radiation
> 3. The patient has a ECOG performance score of 0-1
> 4. The cancer has a CPS score ≥1
> 5. The patient has not received prior systemic treatment

6. Treatment must be undertaken with concomitant platinum based chemotherapy and paclitaxel
7. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks or 400mg every six weeks for a maximum of 24 weeks.

Renewal application – (cervical cancer, metastatic, recurrent, persistent) only from any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of disease progression
2. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent)
3. Prior treatment with pembrolizumab has been for less than 24 weeks or 35 cycles dosed every 3 weeks)

11.6. The Committee recommendation was based on the following:

- The high health need of people with cervical cancer
- The high health need of Māori and pacific people with cervical cancer who are disproportionally affected by cervical cancer with higher incidence rates, more advanced disease at diagnosis and higher mortality from cervical cancer compared to the wider New Zealand population.
- The high-quality evidence showing the health benefit of pembrolizumab in combination with chemotherapy for people with cervical cancer.

Discussion

Māori impact

11.7. The Committee discussed the impact of funding pembrolizumab in addition to chemotherapy, with or without bevacizumab in the treatment of persistent, recurrent or metastatic cervical cancer on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori are disproportionally affected by cervical cancer, with higher incidence of disease, more likely to be diagnosed with advanced cancer and have higher mortality.

11.8. The Committee noted Māori have a lower attendance rate for cervical screening, the attendance rate for cervical screening in Māori was found to be 54.9% in comparison to 74.4% in other women (Best Practice Advocacy Centre, 2023).

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

11.9. The Committee noted Pacific peoples have a lower attendance rate for cervical screening, the attendance rate for cervical screening in Pacific peoples was found to be 55.7% in comparison to 74.4% in other women (Best Practice Advocacy Centre, 2023).

11.10. The Committee noted that Pacific peoples have a higher rate of cervical cancer incidence and mortality than European/Other women 6.1 vs 5.7 and 3.5 vs 1.3 per 100,000 respectively, and a lower screening rate (Ministry of Health, 2020. National Cervical Screening Programme Annual Report 2017).

11.11. The Committee also noted that individuals of rural practices received fewer tests, investigations, prescriptions, and cervical smears than urban patients, but similar rates of referrals (Ministry of Health. 2004. A Comparison of Primary Health Care provided by Rural and Non-rural General Practices: NatMedCa).

Background

11.12. The Committee noted pembrolizumab has been considered by PTAC and other Specialist Advisory Committees for a range of other cancers. The Committee noted bevacizumab has been considered for the treatment of cervical cancer and recommended with a low priority by PTAC in August 2015.

Health need

11.13. The Committee noted early-stage cervical cancer is often asymptomatic and may be diagnosed during a routine screening or pelvic examination. Locally advanced cervical cancer is more likely to present with symptoms such as irregular vaginal bleeding, postcoital bleeding, and vaginal discharge in advanced disease, women may experience lower limb oedema, flank pain, as well as pelvic or lower back pain (Pang et al JCO Oncol Pract. 2022;18:417-22). Additionally, bowel and/or bladder related complaints such as changes in pressure or the passage of urine and/or faeces through the vagina indicate invasion of the bladder and rectum respectively (Burmeister et al. Tumour Virus Res. 2022; 13: 200238).

11.14. The Committee noted cervical cancer is the fourth most common female cancer worldwide and results in over 300,000 deaths globally. A causative agent of cervical cancer is persistent infection with high-risk subtypes of the human papillomavirus (HPV). Persistent infection with high-risk HPV types is responsible for up to 99.7% of cervical cancer cases, with a particularly higher prevalence in women younger than 25 years. Cervical cancer is a largely preventable disease and early-stage detection is associated with significantly improved survival rates (Burmeister et al. Tumour Virus Res. 2022; 13: 200238).

11.15. The Committee considered that prevention through vaccination as well as increased screening rates would be beneficial. The Committee considered high rates of screening and vaccination of people who have had genital warts, sex workers and individuals requiring immunosuppressant drugs would be beneficial in preventing cervical cancer. The Committee noted that Māori and Pacific people are overrepresented in sex workers in New Zealand and sex workers have an increased risk of HPV infection and cervical cancer.

11.16. The Committee noted the 2019 Best Practice Advocacy Centre, HPV vaccination: getting the programme back on track report that noted in New Zealand there was a 67% coverage for females born in 2003. The lowest rate of vaccination was in European/Others (65%), with higher rates in Māori (67%), Asian (71%) and Pacific peoples (73%).

11.17. The Committee considered increasing the age of funded HPV vaccination to match other countries including Canada and the USA would be beneficial in preventing cervical cancer cases. The Committee considered a funding application for increasing the age of HPV vaccination in New Zealand to 45 should be reviewed in the future.

11.18. Cervical cancer mainly occurs in women over 35 years old and is less common in women under 25. Most cervical cancers are diagnosed in women under 60 years old (Te Aho o Te Kahu).

11.19. The Committee noted Klugel et al Int J Womens Health. 2017:9:795-805 that reported individuals with gynaecologic malignancies, especially cervical cancer, had a very high prevalence of psychiatric symptoms including depression (33%-52%). Variables including socioeconomic deprivation, sexual inactivity, absence of a partner, and physical symptoms were correlated with an increased risk.

11.20. The Committee noted the rate of diagnosis with cervical cancer between 2017-2021 (rate per 100,000 and age-standardised to the World Health Organization's standard world population) was higher in Māori and Pacific peoples, with a rate of 4.72 and 4.19 respectively compared with 3.15 in European/Other (Te Whatu Ora Cancer web tool).

11.21. The Committee noted that in addition to the higher rate of disease, between 2007- 2016 Māori and Pacific people were more likely to be diagnosed with advanced disease with 20% and 25% respectively diagnosed at an advanced disease compared with 17% in New Zealand European/Other (Gurney et al, N Z Med J. 2020;133:43-64).

11.22. The Committee noted the number of deaths from cervical cancer between 2017-2021 (rate per 100,000 and age-standardised to the World Health Organization's standard world population) was 1.67 and 1.07 for Māori and Pacific people respectively compared to 0.72 in European/Other (Te Whatu Ora Cancer web tool).

11.23. The Committee noted the five-year survival rate from cervical cancer in New Zealand between 2010 - 2014 was 67.4% (Allemani et al. Lancet. 2018;391:1023-75).

11.24. The Committee noted the CTAC October 2023 record regarding programmed death ligand 1 (PD-L1) testing in New Zealand. The Committee noted considerations that many laboratories in New Zealand do not have the capability to undertake testing, The Committee noted previous considerations that the assay was affected by many variables and that standardisation of testing was necessary otherwise it could cause inequity in access to treatments the individual might benefit from. The Committee noted the suitability of available tests varies between tissue types, and recommended Pharmac seeks further advice of testing in the context of cervical cancer.

11.25. The Committee noted approximately 22-96% of cervical cancers were positive for PD-L1 (Liu et al Front Pharmacol. 2019; 10: 65, Santoro et al. Gynecol Oncol. 2024:184:57-66).

11.26. The Committee noted that KEYNOTE-826 reported 91% of recurrent or metastatic cervical cancer cases have a PD-L1 CPS score of 1 or greater.

11.27. The Committee noted a review of individuals with breast cancer and genealogical cancers and their family caregivers, reported for family caregivers that the burden of caring for their relatives is associated with a significantly reduced physical and psychological health (Awadalla et al. BMC Cancer. 2007;7:102).

11.28. The Committee noted a retrospective cohort study (McLeod et al. Aust N Z J Public Health. 2010;34:193-9) of 1911 women (344 Māori and 1567 non-Māori) identified from the New Zealand Cancer Register with cervical cancer between 1996 and 2006, reported Māori women had higher receipt of total hysterectomies, and similar receipt of radical hysterectomies and brachytherapy as primary treatment, compared to non-Māori women (age and stage adjusted). Over the cohort period, Māori women had poorer cancer specific survival than non-Māori women (mortality hazard ratio (HR) 2.07, 95% confidence interval (CI): 1.63-2.62). From 1996 to 2005, the survival for Māori improved significantly relative to non-Māori. The Committee further noted Thomson et al N Z Med J. 2009;122:39-47 that reported successful strategies for improving screening coverage among Māori women in deprived areas providing evidence that such disparities are not immutable.

11.29. The Committee noted attendance rate for cervical screening in Māori and Pacific people was found to be 54.9% and 55.7% respectively, in comparison to 74.4% in other women (Best Practice Advocacy Centre, 2023). Women who do not regularly participate or have never participated in cervical screening programmes, tend to be diagnosed in the more advanced stages (Best Practice Advocacy Centre, 2023).

11.30. The Committee noted a New Zealand study of Pacific women (Brewer et al. Lancet Reg Health West Pac. 2022:28:100551) reported several challenges for Pacific women to access screening including personal privacy and confidentiality, accessing healthcare, and knowledge around the cervical screening and its use.

11.31. The Committee considered there might more challenges for women in rural areas. The Committee noted the historical NatMedCa study of contacts in NZ general practices nationally reported individuals of rural practices received fewer tests, investigations, prescriptions, and cervical smears than urban patients, but similar rates of referrals (Ministry of Health. 2004. A Comparison of Primary Health Care provided by Rural and Non-rural General Practices: NatMedCa). The Committee noted studies that reported poorer survival from cancer (all combined, prostate, cervical) has been reported for remote areas of New South Wales (Jong et al Med J Aust. 2005;182:13-4), and for rural areas in France (Pozet et al Lung Cancer. 2008;59:291-300), compared with urban areas.

11.32. The Committee noted the treatment paradigm for cervical cancer were published in 2018 by European Society of Gynaecological Oncology (ESGO) jointly with the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP) and updated in 2023 (Cibula et al. Int J Gynecol Cancer. 2023;33:649-66).

11.33. The Committee considered advanced cervical cancer to be very severe with prolonged symptoms, terminal complications, and limited treatment options.

Health benefit

11.34. The Committee noted pembrolizumab is an immune checkpoint inhibitor, which binds to the PD-1 receptor on T-lymphocytes, blocking the effects of the PD-L1 and PD-L2 ligands. This exposes the tumour cell to the immune system.

11.35. The Committee noted the evidence for bevacizumab as a monotherapy was reviewed by PTAC in August 2015. PTAC noted the Tewari et al N Engl J Med 2014;370:734-43 study that reported an increase in the overall survival by 3.7 months, however considered side effects may cause significant health loss which needs to be balanced against potential benefit. The Committee noted the updated Tewari et al Lancet 2017; 390: 1654-63 that reported the final analysis of primary objectives randomised, controlled, open label study. The study reported bevacizumab increased overall survival by 3.5 months (16.8 vs 13.3 months, p=0.007) with no difference in post progression survival. The study reported an increase in grade three fistulae of 6% vs 1% in the bevacizumab group compared to control respectively.

11.36. The Committee noted the KEYNOTE 826 trial, a double-blind, randomised phase 3 trial in people with persistent, recurrent, or metastatic cervical cancer. The results of the trial were reported in the following publications up to a medium follow up of 39.1 months:

- Columbo et al. N Engl J Med 2021;385:1856-67.
- Tewari et al. J.Clin Onc.2022, 40.16
- Monk et al. J Clin Onc.2023, 41.16 suppl5500

11.37. The Committee noted the following results were reported at a median follow up of 39.1 months:

11.37.1. In the pembrolizumab plus chemotherapy group 63.8% received bevacizumab, whilst in the placebo plus chemotherapy group 62.5% received bevacizumab.

11.37.2. In the PDL-1 combined positive score (CPS) ≥1 group the median overall survival was 28.6 vs 16.5 months in the pembrolizumab versus placebo group respectively, and progression free survival median of 10.5 versus 8.2 respectively. Overall survival hazard ratio of 0.60 (0.49-0.74); P < 0.0001.

11.37.3. In the PDL-1 CPS≥10 group the median overall survival was 29.6 vs 17.4 months in the pembrolizumab versus placebo group respectively, and progression free survival median of 10.4 versus 8.1 respectively. Overall survival hazard ratio of 0.58 (0.44-0.78); P < 0.0001.

11.37.4. In the intention to treat population, the median overall survival was 26.4 vs 16.8 months in the pembrolizumab versus placebo group respectively, and progression free survival median of 10.4 versus 8.2 respectively. Overall survival hazard ratio of 0.63 (0.52-0.77); P < 0.0001.

11.38. The Committee noted the objective response rate remained higher in the pembrolizumab-chemotherapy arm compared with the placebo-chemotherapy across all groups (CPS≥1, CPS≥10 and intention to treat) irrespectively of PDL-1 score. The Committee considered the responses were durable over longer follow up.

11.39. The Committee noted there was a high imaging requirement, with seven scans undertaken in the first year, followed by one every 12 weeks. The Committee considered this was not representative of the New Zealand setting and was higher than the number of scans an individual would receive.

11.40. The Committee noted there was no head-to-head analysis of people treated with pembrolizumab with or without bevacizumab in the trial.

11.41. The Committee noted the trial did not investigate if the health benefit differed based on disease location for example individuals with persistent or metastatic cancer. The

Committee noted that local recurrence included all the of pelvis, where distal recurrence included those with disease present in the lymph nodes. The Committee considered it was unlikely there would be a difference in health benefit based on location.

11.42. The Committee considered the number of people with a CPS≥1 in the trial would be representative of the New Zealand population.

11.43. The Committee considered the KEYNOTE 826 trial evidence was of high quality, with very few participants lost to follow up, and a broad range of ethnicities and countries included in the trial.

11.44. The Committee noted Monk et al. Lancet Oncol. 2023;24:392-402 that reported the patient-reported outcomes (PRO) of the KEYNOTE 826 trial. The Committee noted that the addition of pembrolizumab did not negatively affect health related quality of life.

11.45. The Committee noted the following studies:

- Nishio et al. Cancer Sci. 2022;113:3877-87
- Chung et al J Clin Oncol. 2019;37:1470-78
- Frenel et al. J Clin Oncol. 2017;35:4035-41.

11.46. The Committee noted Tewari et al. JAMA Oncol. 2024;10:185-92 that reported a subgroup analysis of the final results of the KEYNOTE 826 study. The Committee noted the overall survival and progression free survival favoured pembrolizumab across all subgroups. The Committee noted the overall survival hazard ratio (HR) in the CPS≥1 population with bevacizumab (HR, 0.62; 95% CI 0.45, 0.87) and without bevacizumab (HR, 0.67; 95% CI 0.47, 0.96) and in the intention to treat population with bevacizumab (HR, 0.63; 95% CI 0.47, 0.87) and without bevacizumab (HR, 0.74; 95% CI 0.53, 1.04). The Committee considered that whilst the study reported the addition of bevacizumab to pembrolizumab was beneficial, the confidence intervals were very wide, and the KEYNOTE 826 study was not powered to analyse these subgroups. Therefore, the Committee considered there was insufficient evidence of any additional benefit from the addition of bevacizumab over pembrolizumab alone. The Committee noted the study did not analyse if the addition of bevacizumab to pembrolizumab affected the number or severity of adverse events. The Committee noted the limitations of utilising this subgroup analysis in the economic modelling of combined pembrolizumab with bevacizumab therapy.

11.47. The Committee noted Zhai et al. BMC Geriatr. 2024;24:32 that reported the case report of an individual who developed hemophagocytic lymphohistiocytosis (HLH) after treatment with pembrolizumab and bevacizumab. A systematic review of 52 cases of immune checkpoint inhibitor related HLH reported HLH often occurred within the first two treatment cycles and approximately 20% of these patients had a history of autoimmune-related disease. The Committee noted HLH had a high mortality rate.

11.48. The Committee considered there would be an increase in adverse events from the addition of bevacizumab, including the risk of rectalvaginal fistulae. The Committee noted PTAC in August 2015 had noted '*treatment with bevacizumab was also associated with an increased incidence of adverse events, most notably hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%). The Committee considered that these side effects may cause significant health losses and costs.'*

Suitability

11.49. The Committee considered there would be increased travel for the individual and their whānau due to more scans, infusions, and clinic visits if pembrolizumab were funded for the treatment of cervical cancer.

11.50. The Committee considered that many might be contraindicated for bevacizumab use, including in individuals that might have evidence of proximal disease where there may be a risk fistulae formation. The Committee noted approximately 65% in the KEYNOTE 826

trial received bevacizumab in combination with pembrolizumab. The Committee considered this might be applicable to the New Zealand population if both agents were funded.

11.51. The Committee considered that some tissues are harder to analyse for PDL-1 CPS and results could vary greatly. The Committee noted testing for cervical tissue is performed privately.

Cost and savings

11.52. The Committee considered there would be an increase in the number of people requiring infusions if pembrolizumab and/ or bevacizumab were funded for cervical cancer. The Committee considered would increase pressure on already stretched infusion services.

11.53. The Committee considered there would be additional pressure on radiology and oncology clinics as more visits would be needed due to improved cervical cancer survival.

11.54. The Committee considered there would be additional pressure on pathology laboratories due to the requirement of PD-L1 testing.

11.55. The Committee noted a side effect of bevacizumab treatment was fistulae, which are complicated to clinically manage, significantly affect the individuals quality of life and may require surgical intervention.

11.56. The Committee noted the high rate of treatment completion reported in clinical trials. The Committee considered that the majority of people receiving treatment with either pembrolizumab monotherapy or pembrolizumab with bevacizumab combination therapy would receive all 35 cycles.

11.57. The Committee considered cisplatin and paclitaxel remain the standard of care for treating cervical cancer. The Committee considered people contraindicated to these treatments would receive carboplatin. The Committee considered most people would receive second line chemotherapy after first line progression.

11.58. The Committee considered 62.3% of people with cervical cancer cases would have an ECOG score of 0-1 (Alholm et al. Gynecologic Oncology 2021;161:422-8).

11.59. The Committee considered pembrolizumab treatment would be palliative, and people are likely to receive chemotherapy following progression on immunotherapy.

11.60. The Committee noted that if funded the number of people treated with pembrolizumab with or without bevacizumab would increase between year 1 and year 2 of treatment and would then remain static, due to a prevalent group requiring treatment.

11.61. The Committee considered that people with a PD-L1 <1 would likely receive monotherapy with bevacizumab if both agents were funded.

11.62. The Committee noted that over time there has been a decline in the number of cervical cancer cases. The Committee considered there is currently an increase in immigration from countries without routine HPV vaccination and screening and therefore the rates of cervical cancer are likely to increase. The Committee also considered rates of screening and vaccinations were decreasing in New Zealand which could affect rates in the future.

Funding criteria

11.63. The Committee noted the objective response rate remained higher in the pembrolizumab-chemotherapy compared with the placebo-chemotherapy across all groups (CPS≥1, CPS≥10 and intention to treat) irrespectively of PDL-1 score. The Committee noted a very small number with a CPS≤1 was included in the study and considered it appropriate to restrict funding to individuals with a CPS≥1.

Summary for assessment

11.64. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for pembrolizumab without bevacizumab if it were to be funded in New Zealand for persistent, recurrent or metastatic cervical cancer. 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 persistent, current or metastatic cervical cancer, with a PD-L1 CPS score of 1 or greater, who have not received prior systemic therapy in the recurrent or metastatic setting.
Intervention	Pembrolizumab, 200mg every three weeks • Treatment continued until treatment progression or unacceptable toxicity, for a maximum of 35 cycles In combination with six cycles of either: • paclitaxel at 175mg/m^2 with cisplatin 50mg/m^2; or • paclitaxel at 175mg/m^2 with carboplatin AUC 5mg/mL/min
Comparator(s)	Platinum-based chemotherapy, comprised of either: • paclitaxel at 175mg/m^2 with cisplatin 50mg/m^2; or • paclitaxel at 175mg/m^2 with carboplatin AUC 5mg/mL/min
Outcome(s)	Improved progression-free survival: • KEYNOTE-826 reported that pembrolizumab-chemotherapy was associated with improved PFS compared to placebo-chemotherapy (HR, 0.66 [95% CI, 0.47, 0.92]) (Tewari et al. J.Clin Onc.2022,40.16) Improved overall survival: • KEYNOTE-826 reported that pembrolizumab-chemotherapy was associated with improved OS compared to placebo-chemotherapy (HR, 0.67 [95% CI, 0.47, 0.96]) (Tewari et al. 2022) •
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Population	People with recurrent or metastatic cervical cancer, with a PD-L1 CPS score of 1 or greater, who have not received prior systemic therapy in the recurrent or metastatic setting.
Intervention	Pembrolizumab, 200mg, **and bevacizumab 15mg/kg**, every three weeks • Treatment continued until treatment progression or unacceptable toxicity, for a maximum of 35 cycles In combination with six cycles of either: • paclitaxel at 175mg/m^2 with cisplatin 50mg/m^2; or • paclitaxel at 175mg/m^2 with carboplatin AUC 5mg/mL/min
Comparator(s)	Platinum-based chemotherapy, comprised of either: • paclitaxel at 175mg/m^2 with cisplatin 50mg/m^2; or • paclitaxel at 175mg/m^2 with carboplatin AUC 5mg/mL/min
Outcome(s)	Improved progression-free survival: • KEYNOTE-826 reported that pembrolizumab-chemotherapy was associated with improved PFS compared to placebo-chemotherapy (HR, 0.58 [95% CI, 0.47, 0.71]) (Monk et al. J Clin Onc.2023, 41.16_suppl5500) Improved overall survival: • KEYNOTE-826 reported that pembrolizumab-chemotherapy was associated with improved OS compared to placebo-chemotherapy (HR, 0.60 [95% CI, 0.49, 0.74]) (Monk et al. 2023)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

12. Pembrolizumab combination therapies for 1L treatment of advanced clear-cell renal cell carcinoma: Pembrolizumab + axitinib (P-001985) Pembrolizumab + lenvatinib (P-001986)

Application

12.1. The Committee reviewed applications for lenvatinib or axitinib in combination with pembrolizumab in the treatment of advanced renal cell carcinoma (RCC).

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

Recommendation

12.3. The Committee **recommended** that lenvatinib in combination with pembrolizumab for the treatment of renal cell carcinoma be funded with a **low priority**, subject to the following Special Authority criteria:

> **INITIATION – Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months
> All of the following:
> 1. The patient has metastatic renal cell carcinoma; and
> 2. The patient is treatment naïve; and
> 3. The patient has good performance status (ECOG grade 0-2); and
> 4. The disease is of predominant clear cell histology; and
> 5. Any of the following:
> 5.1. Haemoglobin level < lower limit of normal; or
> 5.2. Corrected serum calcium level > 10mg/dL (2.5 mmol/L); or
> 5.3. Neutrophils > upper limit of normal; or
> 5.4. Platelets > upper limit of normal; or
> 5.5. Interval of < 1 year from original diagnosis to the start of systemic therapy; or
> 5.6. Karnofsky performance score of less than or equal to 80
>
> **CONTINUATION -Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Treatment remains appropriate.

12.3.1. The Committee made this recommendation based on the following:

- The high unmet health need of those with advanced RCC
- The evidence that lenvatinib in combination with pembrolizumab offers a health benefit.

12.4. The Committee **recommended** that axitinib in combination with pembrolizumab for the treatment of renal cell carcinoma be funded with a **medium priority** subject to the following Special Authority criteria:

> **INITIATION – Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months
> All of the following:
> 1. The patient has metastatic renal cell carcinoma; and
> 2. The patient is treatment naïve; and
> 3. The patient has good performance status (ECOG grade 0-2); and
> 4. The disease is of predominant clear cell histology; and
> 5. Any of the following:
> 5.1. Haemoglobin level < lower limit of normal; or
> 5.2. Corrected serum calcium level > 10mg/dL (2.5 mmol/L); or
> 5.3. Neutrophils > upper limit of normal; or
> 5.4. Platelets > upper limit of normal; or
> 5.5. Interval of < 1 year from original diagnosis to the start of systemic therapy; or
> 5.6. Karnofsky performance score of less than or equal to 80
>
> **CONTINUATION -Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Treatment remains appropriate.

12.4.1. The Committee made this recommendation based on the following:

- The high unmet health need of those with advanced RCC
- The higher quality of evidence that axitinib in combination with pembrolizumab offers a health benefit compared to lenvatinib.

Discussion

Māori impact

12.5. The Committee discussed the impact of funding pembrolizumab in combination with either lenvatinib or axitinib for the treatment of advanced renal cell carcinoma (RCC) on Māori health areas of focus and Māori health outcomes. The Committee noted the previous considerations of the Cancer Treatments Advisory Committee (CTAC) in July 2023 that noted the higher incidence of cases in Māori, who also present at an earlier age (at an average of 52 years old compared to 63 years old in the general population) (Delahunt et al Urology. 1994;43:300-9).

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

12.6. The Committee noted previous considerations of the CTAC in July 2023 that whilst there was no evidence to suggest a difference in prevalence in Pacific peoples, these individuals may have more comorbidities that exclude them from current therapy options. The Committee also noted previous considerations by CTAC in July 2023 that within New Zealand people living in the most socioeconomically deprived areas have a reduced survival time, independent of the stage of disease compared to those from less deprived areas (Jeffreys et al. Cancer Epidemiol Biomarkers Prev. 2009;18:915-21).

Background

12.7. The Committee noted the CTAC reviewed the treatment paradigm for clear cell RCC in July 2023.

Health need

12.8. The Committee noted the July 2023 CTAC record that discussed the health need of individuals with RCC and previous considerations regarding the use of International Metastatic RCC (mRCC) Database Consortium (IMDC) or Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) scoring as a predictor for prognosis.

12.9. The Committee noted that the IMDC score was predominantly used in practice and in clinical trials. The Committee noted that the scoring system was revalidated after the introduction of immunotherapies (Ernst et al. Eur Urol. 2023;84:109-16).

12.10. The Committee noted that New Zealand data was contributed to the IMDC scoring system however the data was not available to review.

12.11. The Committee noted that the scoring system assumes that everyone with a RCC will eventually be treated with a tyrosine kinase inhibitor (TKI) or immunotherapy, and the scoring system aids with identifying the timing of the treatment.

12.12. The Committee noted the scoring system was used in clinical practice at the time of consideration of first line therapy. The scoring would be used periodically over time to check the score and to assess disease progression.

12.13. The Committee noted that those with a favourable risk score would eventually progress to the intermediate and poor risk group. The Committee considered that the time over which progression occurs would vary but may take 3-4 years.

Health benefit

<u>Lenvatinib in combination with pembrolizumab</u>

12.14. The Committee noted the health benefit of lenvatinib in combination with pembrolizumab was explored in the CLEAR study, a phase three open label trial in individuals with

advanced RCC who had not received prior treatment. The noted the following publications that reported the trial outcomes:

- Motzer et al. J Clin Oncol. 2024 :JCO2301569
- Motzer et al.2023 J. Clin. Oncol; 41;16_suppl 4502
- Motzer et al. N Engl J Med. 2021;384:1289-1300
- Motzer et al Lancet Oncol. 2022;23:768-80
- Choueiri et al. Lancet Oncol. 2023;24:228-38

12.15. The Committee noted the following outcomes at 49 months of follow up:

- Overall survival hazard ratio (HR) was 0.79 (95% CI, 0.63, 0.99).
- The median overall survival (95% CI) was 53.7 months (95% CI, 48.7 to not estimable [NE]) with lenvatinib in combination with pembrolizumab vs 54.3 months (95% CI, 40.9 to NE) with sunitinib; 36-month overall survival rates (95% CI) were 66.4% (95% CI, 61.1, 71.2) and 60.2% (95% CI, 54.6, 65.2), respectively.
- The median progression free survival (95% CI) was 23.9 months (95% CI, 20.8, 27.7) with lenvatinib in combination with pembrolizumab and 9.2 months (95% CI, 6.0, 11.0) with sunitinib (HR, 0.47 [95% CI, 0.38, 0.57]).
- Objective response rate also favoured the combination over sunitinib (71.3% v 36.7%; relative risk 1.94 [95% CI, 1.67, 2.26]).

12.16. The Committee noted at four years of follow up it was reported that grade 3 treatment-related adverse events occurred in 74.1% and 60.3% individuals in the lenvatinib in combination with pembrolizumab and sunitinib arms, respectively.

12.16.1. The Committee noted the trial was unblinded for all agents in the study.

12.16.2. The Committee noted that the primary endpoints were changed during the study, as well as the timings of the interim analyses. The Committee considered that additional statistical advice would be needed to determine the effect of this on the trial results.

12.16.3. The Committee considered that there was a high degree of cross over into an experimental agent after progression on the control arm of the trial.

12.16.4. The Committee considered that there was a high number of adverse events however considered this similar to the numbers in other RCC trials, including sunitinib which is currently funded.

12.16.5. The Committee noted 9.7% and 27.6% of people experienced grade ≥3 hypertension or diarrhoea respectively. The Committee noted the autoimmune related adverse events were not reported separately. The Committee considered the treatment of autoimmune related adverse events were more complicated and required additional health resource to manage compared to those of TKIs.

12.17. The Committee also noted the following publications that reported the phase 1b and phase 2 outcomes of the trial:

- Taylor et al. J Clin Oncol. 2020; 38: 1154-63.
- Hang-Lee et al. Lancet Oncol. 2021;22:946-58

12.18. The Committee considered anecdotal evidence that very few individuals can tolerate the full dose of lenvatinib, and this results in quick dose reduction.

12.19. The Committee noted that in comparison to the axitinib in combination with pembrolizumab studies, less individuals were in the favourable prognostic risk group (27% and 27.2% vs 31.9 and 30.5% respectively) and therefore the population overall were clinically more unwell.

Axitinib in combination with pembrolizumab

12.20. The Committee noted the KEYNOTE-426 study, a phase three unblinded randomised controlled trial which explored the health benefit of axitinib in combination with pembrolizumab in individuals with advanced RCC. The Committee noted the following publications that reported the trial outcomes:

- Plimack et al. Eur Urol. 2023;84:449-45
- Rini et al. J.Clin Onc.2023;41;17_suppl. LBA4501
- Rini et al. N Engl J Med. 2019;380:1116-27
- Powles et al. Lancet Oncol. 2020;21:1563-73

12.20.1. The Committee noted the following outcomes at 43 months of follow up:

- The median study follow-up was 43 (range, 36–51) months.
- Benefit with pembrolizumab plus axitinib versus sunitinib was maintained for an overall survival (crossover-adjusted hazard ratio [HR], 0.73 [95% confidence interval {CI}, 0.60, 0.88]),
- The progression free survival was HR, 0.68 [95% CI, 0.58, 0.80], and objective response rate 60% vs 40%.
- The median duration of response was 24 (range, 1.4+ to 43+) versus 15 (range, 2.3–43+) months in the pembrolizumab plus axitinib versus the sunitinib arm.

12.21. The Committee also noted the following publications that reported the phase 1b outcomes of the trial:

- Atkins et al. Lancet Oncol. 2018;19:405-15
- Atkins et al. Eur J Cancer. 2021;145:1-10.

12.22. The Committee noted the study inclusion criteria were more stringent, with more co-morbidities excluded in the study population, including ischemic events and autoimmune disease, compared to the CLEAR study.

12.23. The Committee considered the statistical design of the study was simpler and potentially more fit-for-purpose than the CLEAR study.

12.24. The Committee noted that the study reported results at the 36-month read out, however the study continued until 43 months. The Committee noted this data was not available. The Committee also noted the overall survival data reported at 36 months was modelled to account for subsequent therapy and cross over, however the unmodelled data was not provided.

12.25. The Committee noted that a higher number of those in the sunitinib arm of the trial went on to receive a PD-1 or PDL1 inhibitor in a subsequent line of therapy.

12.26. The Committee noted 9.1% vs 4.7% experienced grade ≥3 diarrhoea in the axitinib in combination with pembrolizumab group compared to the sunitinib group. The Committee noted the number experiencing grade ≥3 hypertension was 22.1% vs 19.3% respectively.

Pembrolizumab in combination with either lenvatinib or axitinib

12.27. The Committee noted Motzer et al Lancet Oncol. 2022;23:768-80 and Bedke et al. Eur Urol. 2022;82:427-39, which reported the health related quality of life (HRQOL) results of people treated in the CLEAR and KEYNOTE-426 study respectively. No difference in the HRQOL measures between individuals in the lenvatinib or axitinib in combination with pembrolizumab group compared to the sunitinib group were reported.

Health benefit considerations in RCC

12.28. The Committee noted there was a lack of studies that reported the effect of treatment on family and whānau of people with RCC.

12.29. The Committee considered that any combination with an immunotherapy may result in some immune adverse events which are more complicated to clinically manage.

Suitability

12.30. The Committee noted that TKI therapies were administered orally, whilst pembrolizumab was administered via intravenous infusion.

Cost and savings

12.31. The Committee noted that for people with IMDC favourable risk the standard of care was monitoring, with repeat IMDC scoring to identify the most appropriate timing for treatment.

12.32. The Committee considered the majority of people would be treated with a combination immunotherapy/ TKI, or dual immunotherapy treatment if funded. The Committee considered a small number of individuals not eligible for immunotherapy treatment due to pre-existing autoimmune with severe enough consequences would receive sunitinib or pazopanib treatment. The Committee considered there was still a niche population where the use of immunotherapy is contraindicated who may use the currently funded TKIs in first line treatment of RCC.

12.33. The Committee noted and agreed with CTAC's recommendation that currently funded first-line TKIs should be funded second line, if immunotherapy was funded.

12.34. The Committee considered the relative proportions of individuals in each IMDC risk group in the CLEAR and KEYNOTE-426 trials were likely representative of the New Zealand advanced RCC population. The Committee considered there was a lack of descriptive data regarding the New Zealand RCC population and that the CTAC or special interest groups may be able to provide more information.

Funding criteria

12.35. The Committee considered the Special Authority criteria for the treatment of RCC should be altered from a Karnofsky performance score of less or equal to 70 to less or equal to 80 in line with IMDC criteria.

Summary for assessment

12.36. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for pembrolizumab in combination with lenvatinib, if it were to be funded in New Zealand for the first-line treatment of advanced clear cell RCC. 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 previously untreated advanced clear-cell renal cell carcinoma (RCC) who are classified as IMDC intermediate or poor risk.
Intervention	• Pembrolizumab 200mg administered via 30-60min intravenous infusion every three weeks (some may receive six- weekly 400mg) until disease progression, unacceptable toxicity, for a maximum of two years • Oral lenvatinib 20mg once per day Upon disease progression, people would receive second-line treatment with sunitinib or pazopanib as per the comparator arm
Comparator(s)	One of: • Oral sunitinib 50mg once daily for 4 weeks, followed by two weeks 'rest period until disease progression or unacceptable toxicity, for a maximum of two cycles. • Oral pazopanib 800mg taken once per day until disease progression or unacceptable toxicity, for a maximum of three months.
Outcome(s)	• Similar overall survival, possibly confounded by subsequent treatments • Longer progression-free survival, which is likely to be associated with improved health-related quality of life (HRQoL) The HR for death was 0.79 (95% CI 0.63, 0.99), despite slightly shorter median OS (Motzer et al.2023 J. Clin. Oncol; 41;16_suppl 4502) compared to sunitinib. Median PFS was significantly longer, at 23.9 compared to 9.2 months (HR 0.47, 95% CI 0.38, 0.57) (Motzer et al. 2021).
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.	

12.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO table for pembrolizumab in combination with axitinib if it were to be funded in New Zealand for first-line treatment of advanced clear cell RCC. 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 previously untreated advanced clear-cell renal cell carcinoma (RCC) who are classified as IMDC intermediate or poor risk.
Intervention	• Pembrolizumab 200mg administered via 30-60min intravenous infusion every three weeks (some may receive six- weekly 400mg) until disease progression, unacceptable toxicity, for a maximum of two years • Oral axitinib 5mg twice per day Upon disease progression, people would receive second-line treatment with sunitinib or pazopanib as per the comparator arm
Comparator(s)	One of: • Oral sunitinib 50mg once daily for 4 weeks, followed by two weeks 'rest period until disease progression or unacceptable toxicity, for a maximum of two cycles. • Oral pazopanib 800mg taken once per day until disease progression or unacceptable toxicity, for a maximum of three months.
Outcome(s)	• Similar overall survival, possibly confounded by subsequent treatments • Longer progression-free survival, which is likely to be associated with improved health-related quality of life (HRQoL) Median OS was not reported at 5-years follow-up, but the HR for death was 0.67 (95% CI 0.52, 0.84) after adjustment for subsequent therapies (Rini et al. J.Clin Onc.2023;41;17_suppl. LBA4501), compared to sunitinib. Median PFS was also longer, at 15.1 compared to 11.1 months (HR 0.69, 95% CI 0.57, 0.84) (Rini et al. N Engl J Med. 2019;380:1116-27)
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.	