PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 19 and 20 August 2021

This meeting was held via videoconference

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016. Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Chair

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies
Giles Newton Howes

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Chair

1. The role of PTAC, PTAC Subcommittees and meeting records

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and PTAC Subcommittees.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

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

Pharmac considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Previous Meeting Record

2.1. The meeting record of the May 20 & 21 2021 meeting was accepted.

3. Subcommittee Records

Rheumatology Subcommittee (May 2021)

3.1. The Committee noted the record of the Rheumatology Subcommittee meeting held on 14 May 2021.

3.2. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that Pharmac would take into consideration both Committees' point of view in its assessment of this application.

3.3. The Committee noted and agreed with recommendations 2.1, 2.2, 2.3 and 2.4 from the Rheumatology Subcommittee regarding applications to widen access to adalimumab and etanercept for rheumatoid arthritis. The Committee noted these proposals had been considered prior to of the adalimumab request for proposals (RFP) evaluation.

3.4. In regard to the Rheumatology Subcommittee's consideration of widened access to adalimumab and etanercept for rheumatoid arthritis:

3.4.1. The Committee considered these Special Authority criteria amendments would enable better access to biologic treatments and reduce inappropriate corticosteroid exposure. The Committee noted that a subsequent discussion by the Rheumatology Subcommittee had recommended these amendments could be also applied to the indication of psoriatic arthritis.

3.4.2. The Committee noted the discussion regarding the inclusion criteria from four key pivotal trials, and that two of these trials did not require a specific C-reactive protein (CRP) level for study entry. The Committee noted the funding restrictions were used to manage fiscal risk when adalimumab and etanercept were first listed for rheumatoid arthritis, and that the treatment paradigm and pharmaceutical costs have substantially changed since that initial listing.

3.4.3. The Committee noted that removal of CRP from the Special Authority would remove any reference to a biochemical marker from the restrictions. However the Committee noted that as a biochemical marker of arthritis activity, CRP is non-specific. Members noted that the Special Authority required applications to be made by rheumatologists, and considered that treating rheumatologists would be treating such cases (including assessing disease severity) within the scope of specialised practice, and hence, considered the restrictions would be appropriate without specific reference to CRP.

Neurological Subcommittee (May 2021)

3.5. The Committee noted the Neurological Subcommittee record regarding a brand change for primidone. The Committee noted that due to a change in supply availability, this brand change would no longer be occurring.

Cancer Treatment Subcommittee (April 2021)

3.6. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that Pharmac would take into consideration both Committees' point of view in its assessment of this application.

3.7. In regards to Subcommittee record item 6 and CaTSoP's consideration of venetoclax in combination with either azacitidine or low dose cytarabine (depending on the access criteria for azacitidine), for the treatment of newly diagnosed acute myeloid leukaemia ineligible for intensive induction chemotherapy:

3.7.1. The Committee noted and agreed with the Subcommittee's priority recommendations for venetoclax in combination with either azacitidine or low dose cytarabine depending on the access criteria for azacitidine. The Committee noted the improved efficacy and survival benefit for venetoclax in combination with azacitidine and considered that it would be beneficial to fund the more efficacious treatment option.

3.8. With regards to Subcommittee record item 8 and CaTSoP's consideration of osimertinib for the first-line treatment of epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC) and the second line treatment of EGFRm T790M positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy:

3.8.1. The Committee noted it had previously considered osimertinib as a first line treatment for EGFRm NSCLC (August 2020) and recommended it for funding if cost-neutral to current first-line pharmaceuticals. The Committee noted it had also previously considered osimertinib as a second line treatment of EFGRm T790M patients (August 2020) and deferred making a recommendation pending review of additional evidence.

3.8.2. The Committee noted the Subcommittee's recommendation that osimertinib be funded as a first line treatment for EGFRm NSCLC with a high priority within the context of malignancy noting the Subcommittee had considered the improvement in long term overall survival reported by the Flaura trial (Ramalingam et al. N Engl J Med. 2020;382:41-50). The Committee considered this improvement in overall survival represented a meaningful benefit from treatment in the setting of malignancy.

3.8.3. The Committee noted the Subcommittee's recommendation that osimertinib as a second line treatment for EGFR T790M patients be funded with a high priority within the context of malignancy. The Committee noted this was based on evidence of a progression free survival benefit from osimertinib, improvement in overall survival, and suitability compared to systemic chemotherapy. The Committee considered that whilst the AURA3 trial had a point estimate for overall survival consistent with benefit, that the evidence was not compelling, with no statistically significant statistically significant improvement in median overall survival (26.8 versus 22.5 months) even when this was corrected for subsequent crossover events. Members considered however that the AURA3 trial did support an improvement in quality of life associated with osimertinib treatment, and considered this likely due to suitability of osimertinib as an oral treatment with reduced toxicity compared to intravenous chemotherapy (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44). The Committee noted literature indicating a global health-related quality of life (HRQoL) improvement, but considered it was unclear how this translated into health utility (Lee et al. J Clin Oncol. 2018;36:1853-60). The Committee supported the recommendation to restrict usage of osimertinib to once per-patient lifetime.

3.9. In regards to Subcommittee record item 9 and CaTSoP's consideration of lenalidomide in combination with either bortezomib and dexamethasone, or dexamethasone alone for the first-line treatment of transplant eligible or ineligible patients with multiple myeloma:

3.9.1. The Committee noted and agreed with the Subcommittee's recommendations and considered that if any further information were required from PTAC to inform modelling then it would be appropriate for review by PTAC. The Committee considered that although use of lenalidomide outside of Medsafe approved indications was possible via Section 25 of the Medicines Act, it was preferable for the use of these medicines to be consistent with Medsafe approval.

3.10. In regards to Subcommittee record item 10 and CaTSoP's consideration of carfilzomib (once-weekly), pomalidomide (in combination with bortezomib and dexamethasone and pomalidomide (in combination with dexamethasone) for the second-line and third-line treatment of relapsed or refractory multiple myeloma:

3.10.1. The Committee noted that it had previously considered carfilzomib for the treatment of relapsed or refractory multiple myeloma (February 2019), and had recommended funding with a low priority based on evidence and dosing from the ENDEAVOR trial. The Committee noted that it had previously considered pomalidomide in combination with dexamethasone for the 4th line treatment of multiple myeloma (February 2016), and had recommended funding with a low priority.

3.10.2. The Committee noted and agreed with the recommendations by CaTSoP for these treatments and combinations, however considered it important for CaTSoP to indicate priority preference for each agent that could

address the unmet need for patients with relapsed/refractory multiple myeloma in each line of therapy.

3.11. With regards to Subcommittee record item 11 and CaTSoP's consideration of crizotinib and entrectinib for the treatment of ROS1 positive metastatic or locally advanced NSCLC:

3.11.1. The Committee noted it had previously considered crizotinib as a treatment for ROS1 positive metastatic or locally advanced NSCLC (August 2020) and recommended it for funding with a low priority; however the Committee noted it has not previously considered entrectinib treatment for this patient group.

3.11.2. The Committee noted the quality and strength of evidence supporting these treatments was poor; however, noted the Subcommittee's consideration that there was a strong biological rationale supporting likely benefit from treatment. The Committee noted the primary evidence supporting entrectinib was from phase I trials which presented incomplete data from a larger participant cohort, and that the evidence supporting crizotinib was predominantly from a phase II trial that reported improvements in progression free survival and quality of life only, but no overall survival benefit. The Committee considered there was possible reporting bias from the phase I entrectinib evidence, and considered the crizotinib evidence may be more representative of the benefit that could be realised for this patient group. The Committee noted the Subcommittee's consideration that, due to low patient numbers, phase I and II studies were likely the only evidence available about treatment in this population, and randomised controlled trial data is unlikely to become available.

3.11.3. The Committee noted the Subcommittee's recommendations and considered that if any further information based on the extrapolation of benefit from different trials were required to inform modelling, then further review by CaTSoP could be considered.

3.12. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the April 2021 meeting.

Endocrinology Subcommittee (March 2021)

3.13. The Committee noted the record of the Endocrinology Subcommittee meeting held on 30 March 2021.

3.14. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that Pharmac would take into consideration both Committees' points of view in its assessment of this application.

3.15. The Committee noted the recommendations and discussion about micronised progesterone for menopause and cinacalcet for hyperparathyroidism. The Committee noted it was scheduled to discuss these items at this meeting and it would consider the Endocrinology Subcommittee's discussion as part of these separate agenda items.

3.16. In regard to item 10, denosumab for osteoporosis:

3.16.1. The Committee noted the Subcommittee's recommendations regarding denosumab for osteoporosis. The Committee noted that denosumab was listed on the Pharmaceutical Schedule for osteoporosis subject to funding restrictions in 2018, following advice from the Endocrinology Subcommittee and PTAC. The Committee noted this present discussion was a result of a paper from Pharmac staff seeking updated advice on widening access to denosumab.

Bisphosphonates and renal impairment

3.16.2. The Committee noted the Endocrinology Subcommittee considered oral bisphosphonates were contraindicated in patients with renal impairment. The Committee considered that oral bisphosphonates could be used in patients with renal impairment, however noting that according to the Medsafe datasheets.

- the cut-offs for renal impairment are different for alendronate sodium and risendronate sodium
- oral bisphosphonates are not recommended in patients with renal impairment due to lack of clinical data in this patient group, rather than documented harm.

3.16.3. The Committee considered it would have been useful for the Endocrinology Subcommittee to have documented explicit evidence to support the recommendation to change the Special Authority regarding oral bisphosphonates and renal impairment. The Committee considered that, while patients with renal impairment were less likely to have been recruited into studies of oral bisphosphonates, that the Committee had reviewed this area in detail as documented in the PTAC May 2016 meeting record. This review included a number of studies in which the oral bisphosphonates had been used in patients with renal impairment. The Committee was unclear on the view of the Subcommittee on this evidence or whether the Subcommittee was aware of other evidence regarding bisphosphonate use in patients with renal impairment. The Committee considered a reasonable approach is to use caution when prescribing bisphosphonates for patients with renal impairment and to consider a reduction in dose rather than avoid them entirely.

3.16.4. The Committee was supportive of amending the Special Authority however suggested criterion 3.1 could include 'bisphosphonates are contraindicated' and remove reference to eGFR. The Committee considered this would ensure the restrictions wouldn't conflict with other information sources. The Committee considered prescribers would have the flexibility to determine the most appropriate treatment for their patient based on individual patient circumstances and contraindications.

Intolerance to bisphosphonates

3.16.5. The Committee considered it reasonable to fund denosumab for patients both contraindicated and intolerant to bisphosphonates.

3.16.6. The Committee considered up to 30% of patients could have intolerance to oral bisphosphonates. The Committee noted a NICE review which reported up to 50% of patients were not taking oral bisphosphonates after three years and considered this highlighted the impact of intolerance on patient persistence. The Committee considered an economic analysis for denosumab would need to account for the reduced fracture risk for those who receive

denosumab, as the comparator patient group would not currently be on any treatment.

Accessing infusions services

3.16.7. The Committee considered the current inequities in accessing IV zoledronic acid infusions, noting that, although the medication itself is funded, patients are often required to pay for infusions in primary care. The Committee considered many patients would likely receive the first infusion of zoledronic acid while in hospital but would need to receive maintenance doses in primary care settings.

3.16.8. The Committee considered patients already engaged in secondary care services were more likely to be able to access treatment in hospital and therefore avoid paying for infusion costs.

3.16.9. The Committee considered the cost of infusion administration disproportionately affected those in rural areas or from low-income households. The Committee considered Māori and Pacific peoples were also likely to be disproportionately affected.

3.17. In regard to item 11, osteoporosis treatments:

3.17.1. The Committee noted the recommendations regarding osteoporosis treatments. The Committee noted these were not related to a specific application, but that Pharmac staff wished to rationalise and harmonise the treatments funded for osteoporosis on the Pharmaceutical Schedule.

Zoledronic acid

3.17.2. The Committee agreed with the recommendation to open-list zoledronic acid. However it considered that the different presentations were Medsafe-approved for different indications and that clinicians should exercise judgement if considering prescribing zoledronic acid for non-approved indications.

Teriparatide

3.17.3. The Committee noted the recommendation to amend teriparatide to a first-line agent for patients with symptomatic vertebral fractures.

3.17.4. The Committee considered this would be a substantial shift in clinical practice. The Committee noted the Subcommittee considered teriparatide was less effective after an alternative bisphosphonate and should therefore be considered for funding as a first-line agent. The Committee suggested the Subcommittee review supporting literature for this recommendation at its next meeting.

Raloxifene

3.17.5. The Committee noted the recommendation to delist raloxifene.

3.17.6. The Committee considered it was beyond the remit of clinical advisory committees to recommend Pharmac delist treatments unless there was new evidence suggesting a substantial change in benefit-risk profile of a funded treatment.

3.18. In regard to item 12, eplerenone for primary aldosteronism:

3.18.1. The Committee noted the recommendation regarding eplerenone for primary aldosteronism, for patients intolerant to spironolactone. The Committee noted this application had previously been considered by the Cardiovascular Subcommittee and the Committee had recommended Pharmac seek advice from the Endocrinology Subcommittee.

3.18.2. The Committee noted, following the discontinuation of amiloride, patients intolerant to eplerenone had no alternative treatment option.

3.18.3. The Committee was supportive of the recommendation. However, the Committee considered applications could be 'on the recommendation of a specialist' in order to minimise barriers to access in requiring the patient to see a specialist. The Committee noted this was in line with Pharmac's developing Schedule Standards.

4. Matters Arising – Action Points

Discussion

4.1. The Committee requested that action points be properly recorded and carried forward in minutes until completed.

5. Correspondence

5.1. No correspondence recorded.

6. Cinacalcet for primary, secondary and tertiary hyperparathyroidism

Application

6.1. The Committee considered cinacalcet for primary, secondary and tertiary hyperparathyroidism to support Pharmac's assessment of these proposals.

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

Recommendation

6.3. The Committee **recommended** that cinacalcet for primary hyperparathyroidism be funded with a **medium priority** subject to the following Special Authority criteria:

CINACALCET
Initial application - (primary hyperparathyroidism) from any relevant specialist. Applications valid without further renewal for applications meeting the following criteria:
All of the following:
1. Patient has primary hyperparathyroidism; and
2. Either:
   2.1. Patient has hypercalcaemia of >3 mmol/L with or without symptoms; or
   2.2. Patient has hypercalcaemia of >2.85 mmol/L with symptoms; and
3. Patient is not deemed operable, or surgery has failed, or surgery is contraindicated; and
4. Patient has other comorbidities, severe bone pain, or calciphylaxis.

In making this recommendation, the Committee considered:

- The high health need of people with hypercalcaemia with or without symptoms who are not candidates for surgery and the lack of available treatments for this patient group

- That there remained concerns regarding the indirect evidence of benefit from cinacalcet that uses surrogate outcome measures, but that a reduction in serum calcium from cinacalcet should translate into a reduction in hospitalisations (for treatment of symptomatic hypercalcaemia and its complications) and an improvement in quality of life

- The uncertainty around patient numbers for the target group

- The side effect profile of cinacalcet.

6.4. The Committee **recommended** that cinacalcet for secondary hyperparathyroidism be funded with a **medium priority** subject to the following Special Authority criteria:

CINACALCET
Initial application – (secondary or tertiary hyperparathyroidism) from any relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Either:
   1.1. Patient has tertiary hyperparathyroidism and markedly elevated PTH with hypercalcaemia; or
   1.2. Patients has symptomatic secondary hyperparathyroidism with elevated PTH; and
2. Patient is on renal replacement therapy; and
3. Any of the following:
   3.1. Patient has undergone repeated unsuccessful parathyroid exploration with inability to localise residual parathyroid tissue; or
   3.2. Parathyroid tissue is surgically inaccessible; or
   3.3. Parathyroid surgery is not feasible and cinacalcet treatment is to be used as a bridge to kidney transplantation.

Renewal – (secondary or tertiary hyperparathyroidism) from any relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
Either:
1. Both:
   1.1. Following initial treatment with cinacalcet, the patient has had a cinacalcet treatment-free interval of at least 12 weeks; and
   1.2. Cinacalcet is indicated after reassessment of parathyroid function performed at least 6 months after cinacalcet cessation; or
2. A trial of withdrawal of cinacalcet is clinically inappropriate.

In making this recommendation, the Committee considered:

- The evidence consistent with improved mortality from treatment with cinacalcet from a good quality cohort study

- The lack of strong evidence for quality-of-life benefits from cinacalcet

- The high health need of Māori and Pacific peoples with secondary hyperparathyroidism on dialysis who experience health inequities arising from increased incidence of kidney disease and low kidney transplant rates

- The added benefit of another medicine for management of calcium and phosphate in this patient population

- The side effect profile of cinacalcet.

6.5. The Committee **recommended** that cinacalcet for tertiary hyperparathyroidism be funded with a **medium priority** subject to the following Special Authority criteria:

CINACALCET
Initial application – (secondary or tertiary hyperparathyroidism) from any relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Either:
   1.1. Patient has tertiary hyperparathyroidism and markedly elevated PTH with hypercalcaemia; or
   1.2. Patients has symptomatic secondary hyperparathyroidism, elevated PTH; and
2. Patient is on renal replacement therapy; and
3. Any of the following:
   3.1. Patient has undergone repeated unsuccessful parathyroid exploration with inability to localise residual parathyroid tissue; or
   3.2. Parathyroid tissue is surgically inaccessible; or
   3.3. Parathyroid surgery is not feasible and cinacalcet treatment is to be used as a bridge to kidney transplantation.

Renewal – (secondary or tertiary hyperparathyroidism) from any relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
Either:

2. Both:
   1.1. Following initial treatment with cinacalcet, the patient has had a cinacalcet treatment-free interval of at least 12 weeks; and
   1.2. Cinacalcet is indicated after reassessment of parathyroid function performed at least 6 months after cinacalcet cessation; or
3. A trial of withdrawal of cinacalcet is clinically inappropriate.

In making this recommendation, the Committee considered:

- The indirect evidence consistent with improved mortality
- The lack of strong evidence for quality-of-life benefits from cinacalcet
- The side effect profile of cinacalcet
- The added benefit of another medicine for management of calcium and phosphate in this patient population.

6.6. The Committee considered that Pharmac should seek advice from the Nephrology Subcommittee regarding the Special Authority criteria for cinacalcet for secondary and tertiary hyperparathyroidism, and considered that the Nephrology Subcommittee's view on the proposed renewal criteria for patients who may benefit from cinacalcet retreatment following a period off cinacalcet treatment, where appropriate, would be valuable.

Discussion

Background

6.7. The Committee noted the long history of clinical advice regarding cinacalcet for hyperparathyroidism from the Endocrinology Subcommittee, the Nephrology Subcommittee and PTAC, described on the Pharmac Application Tracker items for primary hyperparathyroidism, secondary hyperparathyroidism and tertiary hyperparathyroidism. The Committee noted the following in particular:

- In July 2008, PTAC had recommended that hyperparathyroidism (any cause) be declined for listing in the Pharmaceutical Schedule
- In June 2014, the Endocrinology Subcommittee noted a recommendation from the New Zealand Society of Endocrinology to fund cinacalcet for patients with

primary hyperparathyroidism who have significant/symptomatic hypercalcaemia (>3mmol/L) and cannot be treated surgically

- In December 2014 the Nephrology Subcommittee recommended cinacalcet for listing in the Pharmaceutical Schedule for secondary and tertiary hyperparathyroidism with calciphylaxis with a medium priority
- In May 2016, cinacalcet was listed on the Pharmaceutical Schedule for patients with parathyroid carcinoma and symptomatic calciphylaxis, subject to Special Authority criteria
- In December 2016, the Nephrology Subcommittee reiterated its previous recommendation with regards to proposed Special Authority criteria for cinacalcet for secondary and tertiary hyperparathyroidism
- In March 2018, the Nephrology Subcommittee considered that access to cinacalcet should be widened to include patients with hyperparathyroidism and kidney disease subject to clinical criteria
- In March 2021, the Endocrinology Subcommittee considered it was reasonable for cinacalcet to be funded for people with primary hyperparathyroidism with severe hypercalcemia who are not deemed operable, and have no available alternative treatments; that a reduction in calcium to less than 3.0 mmol/L was clinically meaningful and a critical outcome for the target group of patients; and that it was reasonable to infer, based on the evidence of benefits (including reduction in mortality) from calcium level reduction (from surgery and from the use of cinacalcet in several hypercalcaemic states), that cinacalcet could result in clinically meaningful benefits from a calcium level reduction in people with primary hyperparathyroidism who are not deemed operable.

6.8. The Committee noted that cinacalcet is a modulator of the calcium sensing receptor. It decreases parathyroid hormone levels by increasing the receptor sensitivity to extracellular calcium. The Committee noted that cinacalcet is approved by Medsafe to treat:

- the biochemical manifestations of secondary hyperparathyroidism in adult patients with end stage renal disease, receiving dialysis as adjunctive therapy
- hypercalcaemia in adult patients with parathyroid carcinoma
- primary hyperparathyroidism in adult patients for whom parathyroidectomy is not a treatment option.

6.9. The Committee noted that cinacalcet has long been included within international treatment guidelines and considered no new primary evidence to be available since past reviews of these proposals by the Subcommittees. The Committee considered that the existing clinical trial evidence had been used extensively in meta-analyses and noted that some new meta-analyses and registry descriptive data had been identified.

6.10. The Committee considered that for primary hyperparathyroidism, the estimated number of patients who require hospital care was uncertain and that there was a lack of agreement in the estimates of benefit across outcome measures. The Committee

considered similarly that for secondary and tertiary hyperparathyroidism there was also a lack of agreement in the estimates of benefit across outcome measures.

Primary hyperparathyroidism

6.11. The Committee noted that primary hyperparathyroidism is caused by over-activity of one or more parathyroid glands and can be caused by carcinoma, adenoma or hyperplasia. The Committee considered that patients with primary hyperparathyroidism can have a high health need due to hypercalcaemia and that symptomatic hypercalcaemia can cause symptoms such as cognitive impairment, and mobility disorders, which can significantly affect older adults.

6.12. The Committee noted there is a clear consensus that surgical parathyroidectomy is preferred for optimal management of primary hyperparathyroidism, offering a high rate of cure, with minimally invasive surgery with low rates of complications. The Committee considered that most patients would consent to this surgery and that very few patients with primary hyperparathyroidism would be deemed unsuitable for surgery. The Committee considered patients may be deemed unsuitable because surgery is not recommended or feasible e.g. due to anaesthesia concerns or in patients for whom surgery is challenging due to neck size. The Committee considered that Māori and Pacific peoples may be more likely to have surgical contraindications and therefore not receive surgical treatment.

6.13. The Committee noted that the Endocrinology Subcommittee had defined a group of people with primary hyperparathyroidism with severe hypercalcemia who are not deemed operable for whom funded treatment with cinacalcet would be appropriate and that Pharmac staff proposed Special Authority criteria to target this group. The Committee considered that this target group would include the small number of patients who met surgical criteria but were not suitable for, or did not consent to, surgery.

6.14. The Committee noted the Endocrinology Subcommittee's conclusions regarding the efficacy of cinacalcet for primary hyperparathyroidism in March 2021 (meeting record paragraphs 9.14 to 9.20) following the Subcommittee's consideration of evidence from Collier et al. (Endocr Pract. 2019;25:335-9), Ng et al. (Endocr Connect. 2020;9:724-35), Reid et al. (J Clin Endocrinol Metab. 2019;104:3692-700) and Kontogeorgos et al. (Scand J Clin Lab Invest. 2020;80:6-13). PTAC members noted that in one meta-analysis (Ng et al. 2020), the aggregate incidence of nausea or vomiting with cinacalcet was 23%, and members considered that cinacalcet treatment could cause detrimental effects. However, members noted that there was randomised controlled trial evidence of a statistically significant health-related quality-of-life benefit from cinacalcet, and in particular in the mental component score of the SF-36, and considered that this could be an important benefit for patients symptomatic hypercalcaemia (Khan et al. Eur J Endocrinol 2015;172:527-35; although the least-squares mean change from baseline in mental component summary score of the SF-36; of 1.6 in cinacalcet group vs -2.7 in placebo group, *P*=0.047, did not in sum (4.3 units) exceed the likely clinically important difference of 5 units.

6.15. The Committee:

- noted the evidence for a mortality benefit from cinacalcet was indirect, and considered the evidence to be of low to moderate quality and poorly defined
- considered the evidence for cinacalcet's biochemical effect (reduction in hypercalcaemia) to be robust

- considered the evidence for translation of benefits from cinacalcet into other outcomes to be poor.

The Committee considered that an assumption of a reduction in inpatient care e.g. hospital admissions, was not supported by direct clinical trial reports.

6.16. The Committee noted that the target group was consistent with the definition used in the NICE guidelines for primary hyperparathyroidism in the UK and Wales (NICE, 2019), which recommended cinacalcet if surgery has failed or has been declined in patients with serum calcium greater than 2.85 mmol/L with symptoms or greater than 3 mmol/L without symptoms and recommended the use of bisphosphonates only for secondary osteoporosis. The Committee noted that UpToDate (February 2021) recommended cinacalcet in hyperparathyroidism for non-surgical candidates with hypercalcaemia and/or severe symptoms.

6.17. The Committee considered that its concerns remained regarding the indirect evidence and surrogate outcomes for benefit from cinacalcet in primary hyperparathyroidism. Members noted the randomised controlled trial evidence of a quality-of-life benefit reported by Khan et al. but considered that it remained somewhat unclear whether cinacalcet simply acted as a calcimimetic or could ameliorate symptoms of hypercalcaemia, and if so, what magnitude of benefit was associated with its use. The Committee considered the quality of evidence to be low overall and consisting of expert opinion rather than high-quality clinical trials, but that further high-quality direct clinical trial evidence would not be forthcoming in this area. The Committee noted that cinacalcet acts specifically in this disease state, with biological plausibility supporting extrapolation of the available data for beneficial outcomes, and acknowledged the Endocrinology Subcommittee's view that cinacalcet would be expected to provide benefit in this setting. The Committee noted that there is randomised controlled trial evidence of improvement in quality-of-life measures in primary hyperparathyroidism and considered that this was supported by evidence of benefit in secondary hyperparathyroidism.

6.18. Overall, the Committee noted the uncertain benefits associated with surrogate outcomes in this setting, but considered that a reduction in serum calcium from cinacalcet should translate into a reduction in hospitalisations (for treatment of symptomatic hypercalcaemia and its complications) and an improvement in quality of life (although difficult to quantify). The Committee therefore considered that funding cinacalcet for this small patient group with an unmet health need was pragmatic and reasonable.

6.19. The Committee noted the Endocrinology Subcommittee indicated there were about six to ten new cases per year in New Zealand who would be within the target group. The Committee also noted Pharmac staff's estimate of up to 230 new cases per year, based on international data for age-adjusted incidence and suitability for surgery. The Committee considered that the number estimated by the Endocrinology Subcommittee appeared to be low, but also that the Pharmac staff estimate was likely too high as this included patients not meeting the biochemical criteria in the proposed Special Authority, and many New Zealand patients may otherwise be referred for surgery. The Committee considered that the proposed criteria were for a severe subgroup and it was likely there were only a small number of New Zealand patients who meet these criteria. The Committee noted that 395 parathyroidectomies were performed in New Zealand in 2017-18 although this number would include operations for all types of hyperparathyroidism, of which primary hyperparathyroidism might account for one third.

6.20. The Committee considered that the proportion of patients not having surgery due to patient or clinician choice would be very small. Members noted that the literature-based estimate of the proportion of patients reported to be unsuitable for surgery (10-50%; Pappachan et al. Endocrine 2018;62:174-81) was from an elderly population of which half did not receive surgery due to patient choice, and considered that this estimate identified a wider pool of patients than those targeted by the proposed Special Authority criteria.

6.21. The Committee considered it challenging to confirm numbers for patients requiring hospital care for hyperparathyroidism. The Committee was made aware of Ministry of Health data that indicated there were 301 admissions for hyperparathyroidism (E21 code: Hyperparathyroidism and other disorders of parathyroid gland) in 2017-18 of mean 3.7 days inpatient stay, occurring mostly in females (70%) and with about a third aged over 70 years. However, the Committee considered that this data was not well aligned to the target population as it included all types of hyperparathyroidism, and did not represent the outcomes of a severe group who are unable to have surgery. The Committee considered that a detailed analysis of this admission data would help to clarify the actual number of patients admitted for hospital management of primary hyperparathyroidism without surgery in New Zealand and strongly encouraged Pharmac staff to pursue this to inform their assessment of cinacalcet.

6.22. The Committee considered that bisphosphonates are not a suitable comparator treatment in this setting, as they are generally only used as a short-term treatment for hypercalcaemia, do not directly affect the underlying cause of disease, and are excluded from some guidelines for management of primary hyperparathyroidism. However, members considered that some bisphosphonate use occurs in primary hyperparathyroidism where no alternative treatments are available.

6.23. The Committee considered that cinacalcet would be used as single-agent therapy, replacing inpatient care i.e. bisphosphonates, loop-diuretics, fluids and in-hospital nursing and ancillary care. The Committee noted a Pharmac estimate of 0.09 hospitalisations per year for patients with hypercalcaemia, based on the study by Pappachan et al. (2018). The Committee considered that the estimated hospitalisation rate appeared low and considered that the actual hospitalisation rate would be greater than this, but also noted the lack of published data on hospitalisation rates for this patient group. The Committee considered that a reduction in hospital care was likely and may be a key driver of costs, with potential health benefits (based on indirect evidence) and quality of life improvement. The Committee considered that those patients who do not respond to cinacalcet are a highly comorbid subgroup who would be expected to cease cinacalcet treatment due to treatment being poorly tolerated, increasing sickness, or death.

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

Population	Patients with primary hyperparathyroidism who are not deemed operable, or surgery has failed, or surgery is contraindicated; Patients also have either a) symptomatic disease and serum calcium >2.85mmol/L or b) asymptomatic disease and serum calcium >3.0mmol/L Average age at initiation 72.3 years based on the baseline characteristics in the trial by Khan et al. Eur J Endocrinol 2015;172: 527-35
Intervention	Cinacalcet, mean daily dose 82.7 mg based on Khan et al. (2015)
Comparator(s) (NZ context)	Best supportive care (not bisphosphonates)
Outcome(s)	Reduction in parathyroid hormone and serum calcium vs placebo No change in bone mineral density (BMD) or risk of cardiovascular (CV) events vs placebo Based on reduction in serum calcium (and no change in BMD), could extrapolate to assume: • Improvement in quality of life (symptom amelioration), primarily through improvement in mental components of quality of life • Reduction in risk of mortality (indirect, uncertain) • Reduction in the need for hospitalisations to correct hypercalcaemia

Secondary and tertiary hyperparathyroidism

6.25. The Committee noted that secondary hyperparathyroidism is characterised by excessively high parathyroid hormone levels as a response to prolonged hypocalcaemia or hyperphosphataemia, often due to renal insufficiency. The Committee noted that tertiary hyperparathyroidism develops from long-standing, uncontrolled secondary hyperparathyroidism despite correction (or attempted correction) of hypercalcaemia and hyperphosphataemia, for example in patients with end-stage renal disease of several years' duration.

6.26. The Committee noted that Māori and Pacific peoples with secondary hyperparathyroidism on dialysis have a high health need and experience health inequities arising from increased incidence of kidney disease and low kidney transplant rates. The Committee considered that kidney transplant is an effective treatment for secondary hyperparathyroidism if performed before disease becomes severe and is the preferred treatment option for secondary/tertiary hyperparathyroidism. The Committee noted best supportive care is the current treatment for patients with secondary/tertiary hyperparathyroidism who have had, or are unsuitable for, a kidney transplant. However, the Committee considered that this supportive care is associated with poor outcomes.

6.27. Members noted that cinacalcet therapy for secondary/tertiary hyperparathyroidism has been referred to as ‘medical parathyroidectomy’ due to its therapeutic intent.

6.28. The Committee noted that there was little new evidence of relevance available since cinacalcet was last considered for secondary and tertiary hyperparathyroidism by Pharmac’s clinical advisory committees, and noted that previous concerns were around the estimates of benefit across outcome measures.

6.29. The Committee was made aware of the Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline update, which did not recommend cinacalcet in chronic kidney disease but did recommended cinacalcet as

initial therapy in patients with secondary hyperparathyroidism on dialysis. The Committee noted that KDIGO 2017 did not specifically recommend cinacalcet for tertiary hyperparathyroidism, and noted that cinacalcet is not Medsafe approved for hyperparathyroidism post-transplant but acknowledged that it is used in this setting. The Committee noted that UpToDate (July 2021) did not recommend cinacalcet in chronic kidney disease, however UpToDate did recommend cinacalcet for patients with secondary hyperparathyroidism on dialysis following unsuccessful management of calcium and phosphate levels and does not give advice for tertiary hyperparathyroidism.

6.30. The Committee noted evidence from a large (n=3,526) inception cohort of patients in Sweden with chronic kidney disease in 2006–2012 (both non-dialysis, dialysis and transplanted) with evidence of secondary hyperparathyroidism who were followed up for median 37 months (Evans et al. Sci Rep. 2018;8:2103). The Committee noted that 12% of patients commenced cinacalcet and the authors had reported this treatment was associated with trends towards an all-cause mortality advantage (adjusted odds ratio 0.79; 95%CI: 0.56 to 1.11), ascribed mostly to a reduction in the odds of fatal/non-fatal cardiovascular events (odds ratio 0.67; 95%CI: 0.48 to 0.93).

6.31. The Committee noted evidence from a randomised, open label study in chronic haemodialysis patients (n=45) with severe secondary hyperparathyroidism that explored the effect of cinacalcet on chronic kidney disease-mineral bone disorder parameters including calcium (Susantitaphong et al. Ren Fail. 2019;41:326-33). The Committee noted the authors reported that cinacalcet was associated with a reduction in parathyroid hormone levels and a benefit in bone mineral markers.

6.32. The Committee noted two meta-analyses that included randomised controlled trial evidence and long-term (up to 7 years) observational data for patients on dialysis, which concluded that cinacalcet reduced all-cause mortality vs placebo in secondary hyperparathyroidism (relative risk [RR] 0.91, 95% CI 0.89-0.94, *P* < 0.001; Zu et al. Kidney Blood Press Res. 2019;44:1327-38; hazard ratio: 0.83; 95% credible interval: 0.78–0.89; Lozano-Ortega et al. J Comp Eff Res. 2018;7:693-707).

6.33. The Committee noted a meta-analysis of generally short-term (less than two years' follow-up) randomised controlled trial evidence in patients with secondary hyperparathyroidism in chronic kidney disease, which reported that cinacalcet administration did not reduce all-cause mortality vs placebo (RR = 0.97, 95% CI = 0.89-1.05, *P* = 0.41; Wang et al. Sci Rep. 2018;8:3111). However, members noted that a large proportion of data in the meta-analysis came from one study (EVOLVE) that reported no mortality advantage overall but did report in sub-population analysis a mortality advantage in patients over 60 years of age (The EVOLVE trial Investigators. N Engl J Med 2012;367:2482-94). The Committee has previously noted various issues with the EVOLVE trial including its post-hoc subgroup analyses (PTAC May 2016 record paragraph 8.24).

6.34. The Committee noted evidence from a systematic review and meta-analysis of long-term mortality after parathyroidectomy or medical treatment from cohort studies including over 20,000 chronic kidney disease patients with secondary hyperparathyroidism, which reported a reduction in all-case death (HR 0.72) and in cardiovascular death (HR 0.63) with surgery (Chen et al. Ren Fail. 2016;38:1050-8). Members considered the number of patients who received cinacalcet was likely low given the enrolment to the individual trials could have ceased in about 2013 and that the survival benefit reported for surgery over cinacalcet likely underestimated the benefit of cinacalcet as a medical parathyroidectomy.

6.35. The Committee noted evidence from a meta-analysis of eight randomised controlled trials, which concluded that cinacalcet reduces serum calcium and serum phosphate but not parathyroid hormone parameters in patients with secondary hyperparathyroidism on dialysis and reported no unexpected safety signals with cinacalcet and vitamin D (Xu et al. Int Urol Nephrol. 2019;51:2027-36). Members noted however that a large proportion of data in the meta-analysis was derived from one study which investigated intravenous treatment with another agent.

6.36. The Committee was made aware of observational evidence from the limited European Dialysis Outcomes and Practice Patterns Study (DOPPS) registry compared with real-world descriptive data which suggested an increase in five-year survival with optimal management across several factors including serum albumin (which was key), phosphate, haemoglobin, vascular access and fluids in a population with predominantly secondary hyperparathyroidism on dialysis (Combe et al. BMC Nephrol. 2019;20:81). Members considered cinacalcet may support management of phosphate levels in this setting and that phosphate management was likely associated with a mortality benefit.

6.37. The Committee was made aware of earlier, observational data from the DOPPS registry reporting that very high and very low parathyroid hormone levels were associated with increased mortality in patients on dialysis (HR for death 1.09; Tentori et al. Clin J Am Soc Nephrol. 2015;10:98-109).

6.38. The Committee noted evidence from a randomised trial of different surgical approaches to parathyroidectomy. This study reported substantial changes from baseline in the physical and mental component summary scores of the SF-36 that did not differ for the different types of surgery (Filho et al. Surgery. 2018;164:978-85). However, the Committee considered that this was not direct evidence for an improvement in quality of life with cinacalcet in secondary (or tertiary) hyperparathyroidism, as cinacalcet was not compared to surgery in that study, and that while cinacalcet may be considered a medical parathyroidectomy, any quality-of-life benefit of cinacalcet would be subject to significant uncertainty.

6.39. The Committee considered that the meta-analyses in tertiary hyperparathyroidism were of lesser quality due to their cohort study design constituents, although considered that the large Swedish cohort study reported by Evans et al. (Sci Rep. 2018;8:2103) was of good quality.

6.40. The Committee noted that a small (n=24) randomised cohort study comparing parathyroidectomy with cinacalcet for treating tertiary hyperparathyroidism reported normalised serum calcium levels in 7 of 11 patients (64%) in the parathyroidectomy group and 6 of 13 patients (46%) in the cinacalcet group (*P*=0.44) after five years (Moreno et al. Clin Transplant. 2020;34:e13988). The Committee noted that there were no differences observed in kidney function and the incidence of fragility fractures between both groups.

6.41. The Committee noted evidence from a single centre, retrospective cohort study of patients with tertiary hyperparathyroidism (*N*=83, of which 52 received observation alone, 13 received cinacalcet treatment and 18 received parathyroidectomy), and noted that the main determinant of management was the magnitude of elevated serum calcium (Yang et al. Transplantation 2012;15: 70-6). The Committee noted evidence that reported 38% of transplanted patients had elevated parathyroid hormone levels 9-12 months post-transplant; and of these, 63% were observed and the remainder received cinacalcet with or without surgery (Lou et al. Surgery 2016;159: 172-80). The

Committee considered that this evidence suggests half of this patient group could be managed without an intervention.

6.42. The Committee considered that the evidence for tertiary hyperparathyroidism from small cohort studies added little to the evidence for cinacalcet in this setting.

6.43. Overall, the Committee noted that there was no direct evidence of a mortality benefit from cinacalcet in secondary or tertiary hyperparathyroidism although there was indirect evidence of an association between reduced calcium levels and mortality. The Committee considered that outcomes associated with cinacalcet therapy were good relative to surgical outcomes and that this supported the concept of a mortality benefit from cinacalcet. The Committee considered that a mortality benefit was likely the most plausible outcome for patients with secondary hyperparathyroidism receiving cinacalcet. Members considered that cinacalcet may improve allograft survival post kidney transplant in patients with tertiary hyperparathyroidism, although there was an absence of new data to support this.

6.44. The Committee considered that the side effect profile of cinacalcet is well recognised with 10-30% of patients experiencing gastrointestinal upset that may lead to discontinuation.

6.45. The Committee considered that cinacalcet could appropriately form part of the treatment approach for patients with secondary and tertiary hyperparathyroidism who are on dialysis, used as an extra therapy alongside existing treatments in the paradigm for a multi-modal approach to disease management. The Committee considered that serum calcium and phosphate levels are difficult to manage with currently available treatments, and that cinacalcet may make these easier to manage for patients with chronic kidney disease, with particular impact in the management of patients with secondary hyperparathyroidism.

6.46. The Committee considered that, if cinacalcet was funded for secondary hyperparathyroidism, there may be a desire to access it prior to parathyroidectomy especially in patients who were seeking parathyroidectomy while awaiting a kidney transplant. The Committee considered that concerns regarding general anaesthesia may preclude parathyroid surgery as an option for some patients. The Committee considered that a small group may seek cinacalcet access post-surgery and that some patients may access cinacalcet prior to kidney transplant.

6.47. The Committee considered that cinacalcet treatment would be ongoing for those deemed to be requiring it and receiving benefit from it, however, members noted that cinacalcet may not be needed long-term in patients with tertiary hyperparathyroidism whose elevated parathyroid hormone levels resolve post-transplant. The Committee considered parathyroid hormone levels would resolve post-transplant in about two-thirds of cases. The Committee considered it would be reasonable for cinacalcet to be subject to renewal criteria requiring assessment after a period off treatment to confirm the need for further cinacalcet treatment and appropriately target the intended population. The Committee considered that Pharmac should seek advice from the Nephrology Subcommittee regarding the Special Authority criteria for cinacalcet for secondary and tertiary hyperparathyroidism, and considered that the Subcommittee's view on the proposed renewal criteria for patients who may benefit from cinacalcet retreatment following a period off cinacalcet treatment, where appropriate, would be valuable.

6.48. The Committee noted the Nephrology Subcommittee in 2014 had estimated that approximately 5% of dialysis patients would be eligible for cinacalcet treatment

under the proposed criteria. The Committee considered these were likely to be an underestimate, and that it is possible over 50% of patients on dialysis may fit the proposed Special Authority criteria. The Committee considered that based on the surgery criteria in the proposed Special Authority criteria, cinacalcet may plausibly be used prior to surgery in some patients. The Committee considered that many of those that would benefit from cinacalcet in this setting would be Māori and Pacific peoples.

6.49. The Committee noted Pharmac staff's estimate of patient numbers for tertiary hyperparathyroidism, which assumed approximately 17% of patients developed tertiary hyperparathyroidism after renal transplant (Evenepoel et al. Am J Transplant 2014;14: 2545-55). The Committee considered it was uncertain what proportion of these patients would meet the proposed criteria for cinacalcet and therefore receive treatment, but that an estimate of 25% of these patients requiring cinacalcet was reasonable. The Committee considered that tertiary hyperparathyroidism would resolve itself within 12 months in a proportion of patients, and that the time on treatment would therefore be quite short for some patients.

6.50. The Committee considered that cinacalcet may reduce the number of hospitalisations in patients with secondary and tertiary hyperparathyroidism, but any hospitalisation reduction would likely be small. The Committee considered it was plausible that cinacalcet may provide no additional quality-of-life benefits compared with standard of care in the setting of secondary hyperparathyroidism, noting the complex care required for this comorbid patient population. However, the Committee considered that any quality of life benefits would be valuable to patients on renal replacement therapy.

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

Population	Patients on dialysis with symptomatic secondary hyperparathyroidism and elevated PTH who are unable to receive surgical treatment.
Intervention	Cinacalcet, mean daily dose of 60 mg, based on Nephrology Subcommittee advice in 2014
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Significant reduction in serum calcium and serum phosphate Probable but poorly-defined benefit on mortality (most likely outcome), cardiovascular events and health-related quality of life Very small reduction in the need for hospitalisations to correct hypercalcaemia Improved phosphate management, which may be associated with mortality benefits

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

applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with tertiary hyperparathyroidism where surgery is not an option
Intervention	Cinacalcet, mean daily dose of 70.1 mg, based on dosing in the randomised study by Evenepoel et al. Am J Transplant 2014;14: 2545-55
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Significant reduction in parathyroid hormone, serum calcium and phosphate levels Uncertain benefit on outcomes such as fractures, mortality and cardiovascular events May improve allograft survival Based on reductions in serum calcium and phosphate, could assume this translates to improvement in quality of life and reduction in mortality risk Very small reduction in the need for hospitalisations to correct hypercalcaemia

7. Mirabegron for the treatment of overactive bladder

Application

7.1. The Committee reviewed the clinician application for mirabegron (Betmiga) for the treatment of overactive bladder, in light of changes to the availability of funded medicines for overactive bladder, and new clinical information regarding the management of people with overactive bladder in New Zealand.

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

Recommendation

7.3. The Committee **recommended** that mirabegron for overactive bladder as a second-line treatment be funded with a **high priority,** subject to the following Special Authority criteria:

> **MIRABEGRON - Special Authority for Subsidy**
> **Initial application** from any relevant practitioner. Approvals valid without further renewal unless notified, where patient meets the following criteria:
> All of the following:
> 1. Patient has overactive bladder; and
> 2. Either:
> 2.1. Anticholinergics are contraindicated due to concurrent dementia or cognitive impairment; or
> 2.2. Oxybutynin or solifenacin is not tolerated or is ineffective following a reasonable trial; and
> 3. Mirabegron to be used as monotherapy.

7.3.1. In making this recommendation, the Committee considered that:

- There are a range of issues preventing equitable access to other treatments for overactive bladder e.g. botulinum toxin injections, continence products
- The anticipated discontinuation of oxybutynin would result in a lack of accessible second-line treatment options for overactive bladder

- Overactive bladder significantly affects an individual's health-related quality of life

- Mirabegron is as effective as current funded treatments for overactive bladder (specifically, botulinum toxin injections as second-line treatment)

- Mirabegron may be better tolerated than current funded treatments for overactive bladder, although it is not without risks.

7.4. The Committee recommended that mirabegron be open listed with a **medium priority**.

7.4.1. In making this recommendation, the Committee considered that:

- There are a range of issues preventing equitable access to other treatments for overactive bladder e.g. botulinum toxin injections, continence products

- Botulinum toxin injections may be less suitable for older adults with an increased potential for urinary retention

- The anticipated discontinuation of oxybutynin would result in fewer accessible treatment options for overactive bladder

- Overactive bladder significantly affects an individual's health-related quality of life

- Mirabegron is as effective as current funded treatments for overactive bladder (specifically, solifenacin as first-line treatment or botulinum toxin injections as second-line treatment)

- Mirabegron may be better tolerated than current funded treatments for overactive bladder, although it is not without risks

- Long-term persistence on mirabegron for overactive bladder would be low (38% at one year).

Discussion

7.5. The Committee noted that:

7.5.1. PTAC reviewed the clinician application for mirabegron for the treatment of overactive bladder in August 2019 and recommended that mirabegron be funded only if cost-neutral to oxybutynin, due to a similar health benefit compared to currently funded agents. This recommendation was made in the context of three funded anticholinergic medicines for overactive bladder: oxybutynin, tolterodine and solifenacin.

7.5.2. Pharmac received correspondence in November 2020 from the Canterbury District Health Board and the Urological Society of Australia and New Zealand, who emphasised the unmet clinical need of patients with overactive bladder, considered mirabegon would likely be cost-effective as a second-line treatment, and considered that intravesical botulinum toxin injections (and possibly incontinence products) were valid comparators for mirabegron, although they noted that botulinum toxin is a costly and resource intensive treatment.

7.5.3. In May 2021, PTAC noted the November 2020 correspondence and was made aware that the restrictions for solifenacin had been removed, that tolterodine was discontinued in early 2020 and that the supply of oxybutynin will be discontinued in late 2021. At that time, PTAC noted that the supplier discontinuation of oxybutynin will reduce the appropriate first line treatment options; and considered that additional evidence regarding the place of botulinum toxin, other treatment alternatives and treatment sequencing would be useful in any further assessment of this application and consideration of the appropriate cost-neutral comparator.

7.6. The Committee noted the correspondence received by Pharmac in July 2021, which provided further information to aid Pharmac's assessment of mirabegron and was endorsed by the New Zealand Urology Clinical Directors Group and the New Zealand Section of the Urological Society of Australia and New Zealand.

7.7. The Committee noted that overactive bladder is particularly prevalent in older adults and although it can affect children, the Committee considered that an older population were the focus of this application. Members considered there is a high health need in the frail, elderly population with overactive bladder, whose symptoms may be exacerbated with anticholinergics, particularly those who are at greater risk of delirium. Members noted that increasing rates of prostate cancer diagnosis and that its treatment can result in greater incidence of stress incontinence, but also noted such treatment-related stress incontinence would not respond to treatment with mirabegron (which manages urgency incontinence).

7.8. The Committee noted that a large proportion of people with overactive bladder experience adverse health-related quality of life due to urinary incontinence, which can affect an individual's confidence, ability to go out and socialise, and their employment. The Committee considered that it was unclear how a reduction of incontinence volume, which was used as a key outcome in the clinical trial evidence reviewed previously, translated into a clinically relevant quality of life benefit. The Committee therefore considered that a reduction in the frequency of incontinence was likely more meaningful.

7.9. The Committee noted that solifenacin is commonly the first line pharmaceutical therapy used in the treatment of an overactive bladder and that there has been greater use of solifenacin following removal of its funding restrictions. The Committee considered that the upcoming discontinuation of oxybutynin will result in a lack of accessible second-line treatments for those patients who did not tolerate or respond to a trial of solifenacin. Given the substantial use of oxybutynin in New Zealand for overactive bladder, the Committee noted that its discontinuation would result in fewer accessible treatment options for overactive bladder overall.

7.10. The Committee considered that a range of issues prevent equitable access to other potentially suitable treatments for overactive bladder including specialist assessment and administration of intravesical botulinum toxin injections and surgical treatment options; poor access to pelvic floor physiotherapists; and a lack of funding of incontinence products for mild-moderate cases in many areas of the country, therefore conveying a cost to the patient. Members noted that sacral nerve stimulator implants are not available in the public health system, and considered that private healthcare providers would be unlikely to fund this treatment.

7.11. The Committee noted that mirabegron is a potent but not fully selective beta-3 agonist that relaxes the bladder muscle to alleviate feelings of urgency, and that its mechanism of action is different to that of the anticholinergic medicines oxybutynin

and solifenacin. The Committee noted that mirabegron is not Medsafe-approved and understood there has been no application to Medsafe for this medicine. The Committee noted that mirabegron is recommended in England and Wales as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects (TA290. NICE, 2013). Members noted that mirabegron has been submitted to the United States FDA in combination with solifenacin for overactive bladder.

7.12. The Committee noted the following conclusions reported in evidence for mirabegron and botulinum toxin (onabotulinumtoxinA) from systematic reviews, network meta-analyses and indirect treatment comparisons:

- OnabotulinumtoxinA has been associated with improved outcomes compared with mirabegron, including reductions in the number of micturitions per 24-hour period and the number of incontinence episodes (Lozano-Ortega et al. Urology. 2019;127:1-8). However, mirabegron was associated with a lower risk of urinary tract infections compared with onabotulinumtoxinA.

- OnabotulinumtoxinA may be superior to mirabegron in improving symptoms of urinary incontinence, urgency and urinary frequency in patients with idiopathic overactive bladder (Freemantle et al. BMJ Open. 2016;6:e009122)

- After 12 weeks, 100 units of onabotulinumtoxinA provided greater relief of overactive bladder symptoms compared with most other licensed doses of other pharmacotherapies (Drake et al. BJU Int. 2017;120:611-22)

- Botulinum toxin A improves urge incontinence episodes, urgency, frequency, quality of life, nocturia, and urodynamic testing parameters; mirabegron improves daily incontinence episodes, nocturia, number of daily voids, and urine volume per void (Olivera et al. Am J Obstet Gynecol. 2016;215:34-57)

- Overactive bladder treatment with antimuscarinics, mirabegron and onabotulinumtoxinA all improve health-related quality of life and symptoms, as reported using the overactive bladder questionnaire (OAB-q), beyond the benefits observed with placebo (Johnston et al. Adv Ther. 2019;36:548-62).

- An analysis of treatment patterns and costs among patients with overactive bladder in the United States reported that oral therapies predominate, first-line combination therapy is common and that there is substantial uptake of oral therapy after procedural options e.g. sacral nerve stimulation, percutaneous tibial nerve stimulation, or onabotulinumtoxinA (Kraus et al. Neurourol Urodyn. 2020;39:2206-22). The Committee noted that it had previously considered the cost of botulinum toxin injections including inpatient stay and potentially general anaesthesia, but noted that other treatments such as pelvic floor exercises would too be associated with health system costs.

7.13. The Committee noted that that endpoints in the trial evidence were often combined or used interchangeably, and that in many trials the placebo groups reported substantial responses. The Committee considered that the evidence suggests either mirabegron or botulinum toxin injections are superior to the other, or the reverse, depending on the data used and how it was analysed. However, the Committee considered that this did not confirm the superiority of either treatment, and that mirabegron appears to be as effective as current funded treatments for overactive bladder. The Committee considered that quality-of-life outcomes were clinically

important, however, reductions in frequency of micturition and incontinence were similarly reasonable outcomes to inform cost-effectiveness modelling.

7.14. The Committee considered that a reduction in incontinence frequency of one to two episodes per day may be insufficient for an individual's treatment goals and that it was likely that patients would seek additional therapies i.e. combination treatment with mirabegron and another therapy e.g. solifenacin or botulinum toxin. However, the Committee noted that the focus of the current application and its supporting evidence was mirabegron monotherapy.

7.15. The Committee considered that mirabegron may be better tolerated than currently funded treatments for overactive bladder, and that while it has different side effects to anticholinergic treatments it is not without side effects such as increased rates of hypertension, infection, headache and urinary retention, due to its relatively selective action as a beta-3 agonist. Members noted anticholinergic toxicities include dry mouth and dental hygiene issues that may require dental care at a cost to the patient, and considered that the side effect profiles of these therapies should be reflected in the cost-utility modelling as appropriate.

7.16. Overall, the Committee considered that it would be reasonable for mirabegron to be funded as monotherapy in patients for whom anticholinergics were ineffective or not tolerated, subject to Special Authority criteria that would manage its fiscal risk. The Committee considered that the target group for second-line use of mirabegron was a narrower population with overactive bladder defined in the primary clinical trials previously reviewed for mirabegron.

7.17. The Committee considered that prescribers may opt to use mirabegron for a broader population than just those patients with cognitive impairment, for whom anticholinergic agents may be contraindicated. The Committee considered that open-listing mirabegron would also provide benefits to patients with overactive bladder, and considered that some prescribers would prefer mirabegron over solifenacin due to their similar benefits yet different side effect profiles. The Committee considered that, if mirabegron were open-listed and used in the first-line setting prior to solifenacin, it was likely that it would eventually be used in combination with solifenacin as an add-on therapy as patients sought additional therapy to further improve their symptoms.

7.18. The Committee considered that some patients may proceed to botulinum toxin injections after receiving insufficient benefit from mirabegron and noted that botulinum toxin is given two to three times per year for overactive bladder, either as an outpatient service or an inpatient treatment for patients who require general anaesthetic. The Committee considered that the estimates of patients receiving botulinum toxin in Canterbury DHB (between 86 to 175 patients in the 2019-20 financial year, excluding the 10% receiving general anaesthesia) for overactive bladder would include public and private care and were reasonable to extrapolate to the entire country. The Committee considered that funding mirabegron would delay treatment with intravesical botulinum toxin injections for patients especially if mirabegron were used second-line as monotherapy following solifenacin. The Committee considered that mirabegron may offset the costs of botulinum toxin injections in patients who received mirabegron but did not proceed to botulinum toxin injections, although the estimated number of such cases was uncertain. The Committee reiterated its previous comments that not all patients would have access to intravesical botulinum toxin injections as a sequential therapy in the treatment paradigm for an overactive bladder.

7.19. The Committee considered that if mirabegron were open-listed, the total patient pool who would access it could be one-and-half times the population initiating

treatment with oxybutynin or solifenacin, as mirabegron would be used in the absence of oxybutynin and would be preferred over solifenacin. The Committee considered that, if mirabegron were funded either as a second-line treatment or open-listed, there may be an initial upsurge in patients seeking treatment, due to current people living with overactive bladder and experiencing issues with anticholinergics. Members considered that uptake could be rapid especially among patients currently on treatment, and estimated that two-thirds of the currently funded population may initiate mirabegron treatment within one year of funding. The Committee also noted that perhaps 10% of women experience urge incontinence and thus there would be additional patients who are not currently receiving pharmaceutical treatment for overactive bladder who would likely commence treatment with mirabegron if it was open-listed, but that quantifying the extent of this was difficult.

7.20. The Committee considered that use of either the 25 mg or 50 mg dose will vary depending on individual symptom-related concerns, however, noted that more symptoms may be experienced during the day rather than at night which could determine dosing behaviour and requirements.

7.21. The Committee considered that mirabegron would be an ongoing long-term treatment and that discontinuation would not be expected to occur unless there was intolerable toxicity. However, members noted that PTAC had previously reviewed evidence of 38% persistence at 12 months on mirabegron, and considered that loss of efficacy may drive mirabegron discontinuation rather than toxicity (Chapple et al. Eur Urol. 2017:72;389-99).

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

Population	People with an overactive bladder who are considered intolerant to all other currently funded anticholinergics People with an overactive bladder concurrently with dementia or cognitive impairment who are intolerant to anticholinergics.
Intervention	Mirabegron 25 or 50mg tablet taken once daily for as long as the person receives some clinical benefit. If the patient does not respond, possible subsequent treatment with intravesical botulinum toxin injections (where accessible), otherwise best supportive care
Comparator(s) (NZ context)	Intravesical botulinum toxin injections (where accessible), otherwise best supportive care
Outcome(s)	Reduction in the frequency of micturition and incontinence as reported in the four network meta-analyses (Lozano-Ortega et al. 2019; Freemantle et al. 2016; Drake et al. 2017; Olivera et al. 2016)

7.23. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for mirabegron if it were to be open-listed. This PICO captures key clinical aspects of

the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	All patients with overactive bladder (open listed)
Intervention	Mirabegron 25 or 50mg tablet taken once daily for as long as the person receives some clinical benefit. If the patient does not respond, possible subsequent treatment with intravesical botulinum toxin injections (where accessible), otherwise best supportive care
Comparator(s) (NZ context)	Intravesical botulinum toxin injections (where accessible), otherwise best supportive care
Outcome(s)	Reduction in the frequency of micturition and incontinence, as reported in the four network meta-analyses (Lozano-Ortega et al. 2019; Freemantle et al. 2016; Drake et al. 2017; Olivera et al. 2016)

8. Risdiplam for the treatment of spinal muscular atrophy types I-III

Application

8.1. The Committee considered a supplier application for the use of risdiplam for the first line treatment of symptomatic spinal muscular atrophy (SMA) - types I, II and III, regardless of age, physical status or disease severity.

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

Recommendation

8.3. The Committee recommended that risdiplam for the symptomatic treatment of type I spinal muscular atrophy be listed with a high priority.

8.4. The Committee recommended that risdiplam for the symptomatic treatment of types II and IIIa spinal muscular atrophy (aged 18 years and under) be listed with a medium priority.

8.4.1. In making these recommendations, the Committee considered the high health need for these patient groups and their whānau, the lack of funded treatments, suitability of oral treatment, short term data, and consequences to the health system. The Committee also noted that there is stronger evidence for benefit in type I SMA than types II and III.

8.5. The Committee noted that the SUNFISH trial investigated the use of risdiplam in non-ambulant type III SMA up to the age of 25 years, regardless of age of symptom onset. However, the Committee considered that risdiplam should be funded for type IIIa SMA (symptom onset prior to age three years) for individuals aged under 18 years (regardless of ambulation status).

8.5.1. The Committee made this recommendation noting that nusinersen was recommended for individuals aged 18 years and under with type IIIa and

considered that the SUNFISH trial did not provide evidence of benefit in individuals aged 18 to 25 years.

8.6. The Committee considered that advice should be sought from specialist clinicians on the most appropriate access criteria for risdiplam for the treatment of SMA, including inclusion of types IIIb and IIIc.

Discussion

Health need

8.7. The Committee noted that the most common form of SMA is caused by a defect in the SMN1 gene on chromosome 5, and that 94% of SMA patients have a deletion in exon 7. The Committee noted that the defect is an autosomal recessive deletion which causes an SMN protein deficiency leading to motor neuron degeneration and subsequent disease progression. The Committee also noted that the SMN2 gene adjacent to SMN1 also produces SMN protein, of which 10-15% is functional as most is truncated and rapidly degraded following translation. The Committee noted that individuals vary in the number of copies of SMN2, which can range from 0 to 8.

8.8. The Committee noted that classification of spinal muscular atrophy (SMA) is based on age of onset and maximal motor function achieved: pre-natal type 0 SMA patients achieve no motor function, are unable to sit or roll, and die within weeks of birth; infantile onset type I SMA patients present with symptoms at less than 6 months of age, are unable to sit or roll, and typically die within 2 years; childhood onset type II SMA patients present with symptoms at 6 to 18 months of age, can sit but are unable to walk independently, and survive to adulthood in 70% of cases; childhood onset type III SMA patients present with symptoms before age 3 (type IIIa), older then age 3 (type IIIb) or between 12 and 18 years of age (IIIc), can independently stand or walk but may lose the ability to walk over time, and have a normal lifespan; and adult onset type IV SMA patients present after age 18, have normal or mildly impaired motor function, and a normal lifespan.

8.9. The Committee noted that patients typically experience an acute phase of new onset of weakness, followed by a chronic phase of functional decline, and that the evolution from the acute to chronic phase depends on the SMA type. The Committee noted that SMA is the most common monogenic cause of infant mortality worldwide. The Committee noted that there is no funded treatment for SMA in New Zealand, and that best supportive care for SMA patients includes physiotherapy, nutritional support, respiratory support, orthopaedic support, and palliative care, all of which come as a significant cost to the health system and patients' families.

8.10. The Committee noted that the health need for SMA type I patients is severe, as most do not live past the age of two years. The Committee also noted that SMA types II and III have a poor outlook in terms of mobility, independence, and quality of life; the majority of patients never walk or lose the ability to walk before reaching adolescence or adulthood. The Committee also noted that the lifetime probability of scoliosis surgery in type II SMA patients is approximately 80%, while SMA type IIIa has a risk of approximately 40%, which is strongly associated with the age of onset of loss of ambulation. The Committee noted than for SMA type IIIa, scoliosis surgery is needed in 71% of patients who lose the ability to walk before the age of 10, versus 22% in patients who lose the ability to talk after the age of 10 (Wijngaarde et al. Neurology. 2019;93:e149-e158). The Committee noted that the major cause of morbidity and mortality in SMA patients is respiratory failure.

8.11. The Committee noted that there is also a high health need for family, whānau, and caregivers of SMA patients, and that some families have left New Zealand to seek treatment internationally, such as moving to Australia to access funded treatment, in some cases leaving behind their families and support systems. The Committee considered that only patients belonging to households with the financial means to relocate are able to make the choice to move overseas, and that those with more difficult socioeconomic circumstances would not have this option. The Committee also noted that specialist clinicians have indicated that Māori and Pacific SMA patients present later due to inequities in access to primary care, which must be considered in the context of access criteria relating to age of diagnosis. The Committee noted that there is a wider societal impact relating to SMA patients who move to adulthood due to different healthcare, educational and transport needs for these individuals.

8.12. The Committee noted that there were 74 SMA patients in New Zealand as at March 2019, 36 of whom were under the age of 18. The Committee noted that the point prevalence of SMA in New Zealand is 1.4 per 100,000, and therefore meets Pharmac's working definition for funding a 'rare disorder' (1 per 50,000), and that the incidence is 0.8 per 10,000. The Committee noted that results from new-born screening programmes across nine international programmes reported an incidence of 0.78 per 10,000 (Dangouloff et al. Neuromuscular Discord. 2021;31:574-82). The Committee noted that there is currently no screening programme for SMA in New Zealand and considered that if any SMA treatment were to be funded here, a screening programme would likely be rapidly implemented alongside this. The Committee noted that the carrier mutation frequency for SMA ranges from 1 in 47 to 1 in 90 people globally (Sugarman et al. Eur J Hum Genet. 2012;20:27-32, Pearn j. J Med Genet. 1978;15:409-13).

8.13. The Committee noted that a funding application for nusinersen, which is not currently funded in New Zealand, for the treatment of SMA was reviewed by the Rare Disorders Subcommittee (November 2018 and September 2019) where the application received a high priority recommendation for pre-symptomatic individuals with spinal muscular atrophy and two or three SMN2 copies, and a medium priority recommendation for symptomatic patients with type I, II, and IIIa spinal muscular atrophy. The Committee noted that PTAC reviewed the application in February 2020 and recommended nusinersen be funded with a high priority for both patient groups. The Committee noted that nusinersen is administered intrathecally, thus only has an effect on the central nervous system.

8.14. The Committee noted that risdiplam is a small molecule that modulates SMN2 gene splicing, binding two sites in SMN2 pre-mRNA, allowing full length SMN mRNA and protein to be synthesised and that systemic distribution has been demonstrated in both the central nervous system and peripheral organs in vivo. The Committee considered that this was significant as SMA is a multiorgan disease with cardiac, muscular, respiratory, autonomic nervous system, and metabolic effects. The Committee noted that risdiplam is not yet Medsafe approved for use in New Zealand, and that there is no FDA approval for use in children under two months of age as there is no safety data for this patient group.

Evidence

8.15. The Committee noted that clinical presentation of SMA depends on the number of SMN2 copies an individual patient has. The Committee noted that because risdiplam acts on the SMN2 protein, patients must have 2 or more copies of SMN2 to derive benefit from risdiplam. The Committee noted that risdiplam is a powder that must be mixed into a solution and administered orally once daily, while nusinersen is

administered intrathecally 4-monthly (following loading doses). The Committee considered that oral administration may be more appropriate for patients who have undergone scoliosis surgery, as intrathecal administration may be difficult for these patients. The Committee considered however that adherence with very young children may be an issue, as babies often have reflux or vomit after feeding, but noted that this was not described in the clinical study data for risdiplam.

8.16. The Committee noted that there are four ongoing phase II clinical studies assessing the safety and efficacy of risdiplam in different SMA types: FIREFISH (SMA type I), SUNFISH (SMA types II and non-ambulant type III), JEWELFISH (SMA patients previously treated with other SMA agents), and RAINBOWFISH (genetically diagnosed, pre-symptomatic SMA patients). The Committee noted that only FIREFISH and SUNFISH are relevant to the current consideration for risdiplam. The Committee considered that the minimal clinically important difference variables for outcomes in these trials are mostly uncertain and unvalidated, with the exception of the Hammersmith Infant Neuromuscular Examination (HINE), for which a clinically important difference is considered to be a one-point increase, and the Hammersmith Functional Motor Scale – Expanded (HFMSE), for which a clinically important difference is considered to be more than two points, however the Committee considered that patients and caregivers would likely still consider a one-point increase to be meaningful.

8.17. The Committee noted that FIREFISH is a level 2B phase II open-label, two-part study for those with SMA type I and a confirmed diagnosis of 5q-autosomal recessive SMA with 2 or more SMN2 gene copies (Darras et al. N Engl J Med. 2021;385:427-35). The Committee noted that there were 41 patients enrolled in the study, and that the median age of enrolment was 5.3 months. The Committee noted that the primary endpoint was the proportion of infants sitting unsupported for 5 seconds or more, and secondary endpoints of event-free survival (alive without permanent ventilation), motor milestone achievement, and CHOP-INTEND scale of motor function results.

8.17.1 The Committee noted that at baseline, 95% of patients were able to swallow, 29% were receiving pulmonary care, and that no infants were sitting without support. The Committee noted that the primary endpoint was met after 12 months with 29% of infants in the clinical study being able to sit without support for 5 seconds or longer (90% CI 18% to 43%). The Committee also noted that at 12 months 93% of study participants were alive, which the study compared to a historical cohort with a median time to death of 6 months in SMA type I at less and 3 months age at onset and 11.5 months for greater than 3 months at onset (Finkel et al. Neurology. 2014;83:810-7).

8.17.1 The Committee noted that at 12 months 85% of participants were without the need for permanent ventilation (P<0.0001) compared to the median age of event-free survival of 10.5 months in Finkel et al. The Committee also noted that 90% of participants achieved an increase of at least 4 points in the CHOP-INTEND total score versus a median change of 1.27 points per year in the Finkel et al historical comparison study, and that 56% of FIREFISH participants achieved a CHOP-INTEND score of 40 or greater (P<0.0001), with a median increase of 20 points across all participants.

8.17.1 The Committee noted that 78% of participants were classified as HINE-2 motor milestone responders compared to performance criterion of 12% (P<0.0001). The Committee also noted that 24% of the infants in FIREFISH did not require invasive or non-invasive ventilatory support, 66% received

prophylactic ventilation, and one infant changed from permanent to non-invasive ventilation.

8.17.1 The Committee noted that 95% of infants maintained the ability to swallow, 83% were able to be orally fed (68% by mouth and 15% by mouth in combination with a feeding tube) versus the Finkel et al historical cohort's median age of 6 to 9 months for gastrostomy placement. The Committee also noted that 49% of infants did not require hospitalisation, and that FIREFISH reported a rate of 1.30 hospitalisations per patient year, compared to 7.6 per year in other studies (Chatwin et al. Arch Dis Child. 2011;96:426-32).

8.17.1 The Committee noted that all infants had at least one adverse event, and that 24 had at least one serious adverse event, the most common being pneumonia. The Committee noted that there were no adverse events leading to withdrawal of risdiplam, and that 3 infants died as a result of SMA-related respiratory events which were not considered by the authors to be related to risdiplam treatment. The Committee noted that the most common adverse event in FIREFISH was upper respiratory-tract infection.

8.17.1 The Committee noted updated 24-month results which indicated that the effects of risdiplam are sustained to 24 months (Darras et al. Neurology. 2021;96(15 supplement) conference abstract 4126): 61% of infants were sitting without support for at least 5 seconds and all patients treated with risdiplam who were able to sit at 12 months maintained this ability at 24 months; 83% of infants were event-free at 24 months; 95% of infants were able to swallow; and 34% did not require hospitalisation. The Committee also noted that there were no new safety signals at 24 months.

8.18. The Committee noted that SUNFISH is a level 1B phase II, double-blind, placebo-controlled trial of risdiplam for the treatment of SMA types II or III (non-ambulant; Mercuri et al. Neurology. April 2020;94(15 Supplement): conference abstract 1260). The Committee noted that there were 180 participants enrolled in the trial, and that the median age at enrolment was nine years of age (range from 2 to 25 years). The Committee noted that the primary endpoint was a change in 32-item Motor Function Measure (MFM32) total score at 12 months in relation to maximum score of 96, and that secondary endpoints were motor function, respiratory function, clinical global impression (which assesses the clinician's impression of a patients' mental health state) and patient/caregiver reported outcomes.

8.18.1 The Committee noted that patients enrolled represented a broad clinical range of SMA, with 71% of participants with SMA type II, and 29% with SMA type III who were non-ambulant; all had 2 to 4 copies of the *SMN2* gene. The Committee also noted that the mean MFM32 total score at baseline was 46.11 with a range of 16.7 to 71.9.

8.18.2 The Committee noted that 32% of participants had severe scoliosis at the time of enrolment, and 26% had scoliosis surgery prior to screening. The Committee noted that patients with severe scoliosis and prior scoliosis surgery were excluded from the CHERISH nusinersen study (Darras et al. Neurology. 2019;92:e2492-e2506).

8.18.3 The Committee noted that the least squares mean change from baseline in MFM32 total score was 1.36 in the risdiplam group versus -0.19

in the placebo group, thus a treatment difference of 1.55 (95% CI 0.3 to 2.81; P=0.0156). The Committee considered that the minimal clinically important difference for MFM32 in SMA patients is unclear, but noted that in a congenital muscular dystrophy observational study the minimally clinically important difference in MFM32 score was 2.5 to 3.9 (Le Goff et al. Arch Phys Med Rehabil. 2021;102:604-10).

8.18.4 The Committee noted that the proportion of individuals with a change of 3 or more points in MFM32 score was 38.3% in the risdiplam group and 23.7% in the placebo group, with a treatment difference of 2.35 points (95% CI 1.01 to 5.44). The Committee also noted that respiratory function (as measured by a least squares mean change in baseline in the best percentage-predicted forced expiratory volume) was -5.16 in the risdiplam treatment group versus -3.11 in the placebo group, with a treatment difference of -2.05 (95% CI -6.67 to 2.56).

8.18.5 The Committee noted that the proportion of individuals rated as 'improved' on the clinical global impression scale was 47.5% in the risdiplam group and 40% in the placebo group, with a treatment difference of 1.38 (95% CI 0.70 to 2.47).

8.18.6 The Committee noted that 20% of patients treated with risdiplam experienced at least one serious adverse event, versus 18.3% in the placebo group, and that there were no deaths. The Committee also noted that pneumonia was more common in the risdiplam group versus the placebo group (7.5% versus 1.7%, respectively). The Committee noted that there were no adverse events leading to dose modifications.

8.18.7 The Committee noted that in subgroup analysis that there was a treatment difference for all subgroups except for those in the 18-35 years age group which did not show any difference in MFM32 scores relative to placebo.

8.18.8 The Committee noted unpublished updated 24-month results which indicated that motor function was stable or showed continued improvement during the second year of treatment with risdiplam, but the Committee considered that the treatment effect compared to placebo was not very large (results presented at the Muscular Dystrophy Association conference on March 15-18 2021. Oskoui et al. 2021). The Committee also noted that improvements in motor function were stable over 12 months in those who switched from placebo to risdiplam at 12 months. The Committee also noted that a decrease in adverse events was seen in the second year in both risdiplam, and those in the placebo group who switched to risdiplam.

The Committee noted that 15% of randomised patients in SUNFISH did not contribute to the 24-month updated data, due to restriction measures during the COVID-19 pandemic.

8.19. The Committee considered that the treatment effect of risdiplam in the SUNFISH group was smaller than that of the FIREFISH group. The Committee also noted that the effect of risdiplam does not seem to extend to those over the age of 18 years and considered that for this reason, if risdiplam were to be funded that initiation of treatment should be limited to those aged 18 years and under but advice should be sought from specialist clinicians regarding this criterion.

8.20. The Committee considered that the evidence for the use of risdiplam in types I, II and III (non-ambulant) SMA patients was of good-moderate quality, with good strength of evidence that risdiplam is superior to best supportive care, and non-inferior to nusinersen. The Committee considered that current evidence cannot be used to extrapolate long-term health gain from risdiplam for SMA patients as the data is not mature enough, but that duration of treatment effect is anticipated to be similar to nusinersen, based on current evidence. The Committee also considered that the results from SUNFISH are likely generalisable to ambulant type SMA patients, though there is limited evidence to support this. The Committee considered that treatment should be started as early as possible to prevent or reduce the loss of ambulation.

8.21. The Committee noted than types I, II, and III only are considered in this application, but that SUNFISH only included people with SMA type III if they were non-ambulant, and recent clinical advice has indicated that both those with SMA type III <18 years of age and those who are pre-symptomatic will derive the greatest benefit from treatment. The Committee noted that less health benefit was observed in the 18–25-year-old subgroup in subgroup analyses provided for the SUNFISH trial.

8.22. The Committee noted that there is no direct evidence comparing nusinersen with risdiplam, and considered this likely not ever changing in future. Informally, the Committee compared the nusinersen and risdiplam trials indirectly and considered that apparent effect appeared better with risdiplam than nusinersen, but noted that there were differences in the trials which meant that this indirect comparison would be confounded.

General

8.23. The Committee considered that risdiplam and nusinersen are likely have a similar clinical effect, noting their similar mechanisms of actions, although that risdiplam may provide the benefit of treating systemic effects outside of the central nervous system. The Committee also considered that there are various benefits with oral treatment over intrathecal treatment, such as reduction in the risks associated with intrathecal administration, reduced hospital visits for patients, cultural preferences, and difficulty administering intrathecal injection in those with severe scoliosis or following scoliosis surgery.

8.24. The Committee noted that the Rare Disorders and Neurological Subcommittees discussed in March 2021 how there were currently no available direct comparisons of nusinersen and risdiplam for the treatment of Type 1 SMA. The Subcommittees noted that while small patient numbers make it difficult to accurately compare the two treatments, they considered that with currently available data, it would be reasonable to conclude that risdiplam demonstrates at least the same or similar magnitude of benefit compared with nusinersen in individuals with type 1 SMA, with no informal signals of inferiority (although formal testing for non-inferiority has not apparently been undertaken).

8.25. The Committee noted that a study of the economic burden of SMA reported that the direct costs of SMA are greater than 50-fold higher compared with matched controls (Belter et al. J Mark Access Health Policy. 2020;8:1843277). The Committee considered that while the economic burden of SMA is likely very high in New Zealand, it is unlikely that these results translate directly to a New Zealand context. The Committee noted a systematic review of the cost of illness of SMA that reported that the cost of SMA is high, but variable across countries (Landfeldt

et al. Appl Health Econ Health Policy. 2021;19:501-20). The Committee considered that while SMA treatment costs in Australia may be comparable in some ways to the New Zealand context, SMA patients in New Zealand are not placed on permanent ventilation and are more likely to only receive palliative care. The Committee noted that there is no evidence currently to indicate if the use of risdiplam (or nusinersen) will impact on or reduce the need for best supportive care for patients with SMA over the course of their life. The Committee noted that Pharmac economic modelling around the use of best supportive care was based on assumptions about patients' levels of need diminishing as morbidity decreased with treatment.

8.26. The Committee noted that if risdiplam were funded in the New Zealand there may be a reduction in health sector costs associated with hospitalisations, need for ventilatory support, and gastrostomy placement, but that the cost of these would not be fully offset due to the current price of risdiplam.

8.27. The Committee noted that in Australia the PBAC recommended risdiplam be funded for SMA types I, II and IIIa for those who are under 18 years of age at treatment initiation, if cost-minimised with nusinersen; and that the CADTH in Canada recommended funding of risdiplam, with various conditions.

8.28. The Committee noted that the application for consideration included SMA types I to III. While the evidence for type III was confined to the SUNFISH trial, which only included people who were non-ambulant with SMA type III, the Committee considered that the results from SUNFISH are likely generalisable to ambulant type SMA patients, though there is limited evidence to support this. The Committee considered that treatment should be started as early as possible to prevent or reduce the loss of ambulation. The Committee considered that Pharmac staff should seek advice from specialist clinicians on appropriate Special Authority access criteria, including which types of SMA should be included.

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

<table>
<tr><td>Population</td><td colspan="2">Symptomatic spinal muscular atrophy type I, II and IIIa (both adult and paediatric patients with symptomatic onset of SMA prior to age 18 years).</td></tr>
<tr><td>Intervention</td><td colspan="2">Risdiplam once daily oral dose as determined by age and body weight</td></tr>
<tr><td rowspan="4"></td><td>Age and body weight</td><td>Recommended daily dose</td></tr>
<tr><td>2 months to < 2 years of age</td><td>0.20 mg/kg</td></tr>
<tr><td>≥ 2 years of age (< 20 kg)</td><td>0.25 mg/kg</td></tr>
<tr><td>≥ 2 years of age (≥ 20 kg)</td><td>5 mg</td></tr>
<tr><td>Comparator(s) (NZ context)</td><td colspan="2">Best supportive care</td></tr>
<tr><td>Outcome(s)</td><td colspan="2">• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking)
• Bulbar function (including, for example, swallowing and ability to communicate)
• Ability to feed orally
• Frequency and duration of hospitalisation
• Respiratory function
• Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)
• Need for non-invasive or invasive ventilation
• Stamina and fatigue
• Mortality
• Adverse effects of treatment
• Health-related quality of life</td></tr>
<tr><td colspan="3">Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.</td></tr>
</table>

9. The inconsistencies associated with the current arrangement for paediatric cancer treatment funding

Discussion

9.1. The Committee noted that current funding for paediatric cancer treatments, for the treatment of cancer, not available via the Pharmaceutical Schedule occurs via a notification of medicine use to Pharmac through the use of Rule 8.1b of the Schedule.

9.2. The Committee noted that there are 15 paediatric oncologists and/or haematologists treating approximately 150 new paediatric cancer patients each year in New Zealand. The Committee noted that nearly all of this treatment is delivered in the public health sector. The Committee noted that children are treated according to formal research protocols 35-40% of the time and that a number of these protocols contain medicines that are not approved for funding (outside of Rule 8.1b). The Committee noted that the current access pathway for this patient group involves no substantial delays in being able to prescribe oncology drugs for children, including those medicines that are expensive. The Committee however noted that it was important that all trials of novel protocols would need to be in line with the exemptions for clinical trial provisions of Section 30 of the Medicines Act.

9.3. The Committee noted that some treatments are made available free of charge, either due to use as part of a clinical trial or for particular unapproved medicines

that the supplier provides as free stock. The Committee noted that in general, for clinical trials, it is the standard of care component in the oncology clinical trial that is publicly funded through rule 8.1b of the Pharmaceutical Schedule if necessary. The Committee noted that presently, there are many issues with the presence of, or rescindment of rule 8.1b that were not as evident when Pharmac was established, or when Pharmac took over the cancer medicines budget from DHBs.

9.4. The Committee considered that the status quo funding arrangement has served this patient group very well and has provided good outcomes compared with other OECD countries. In addition, these good outcomes are not influenced by DHB of domicile or ethnicity. The Committee considered that rescinding rule 8.1b would drive inequities, as it would be more reflective of the less accessible status quo funding arrangements for other patient groups.

9.5. The Committee considered that to date, the total drug budget for paediatric oncology is well contained, but new technologies pose a significant financial risk. The Committee understood that paediatric oncologists/haematologists expect that new technologies, such as CAR-T cell therapy would be 'grandparented' within current paediatric cancer treatment funding arrangements if rule 8.1b of the Pharmaceutical Schedule were rescinded.

9.6. The Committee noted that there were many concerns for paediatric oncologists/haematologists regarding any changes to the current arrangement.

9.6.1. The Committee noted that clinicians, patients and whānau would find it difficult if access to medicines considered to be beneficial (according to clinical consensus) was curtailed.

9.6.2. The Committee noted that the primary concern was in relation to timeliness, noting that a 'high' priority clinical advice recommendation for a medicine could still result in significant delays in funding. The Committee noted that time delays of this magnitude would be seen as serious impediments to the maintenance of current childhood cancer outcomes.

9.6.3. The Committee noted that adolescent and young adults with cancer are treated using the access supplied via part 8.1b if treated within the paediatric cancer service.

9.6.4. The Committee noted that whilst this is not a large group of patients, it is a patient group vulnerable to a change in drug availability.

9.6.5. The Committee noted that many paediatric clinical trials involve surrogate outcomes and frequent revisions to the trial protocols and that definitive clinical end-points, such as overall survival differences, often emerge well after the investigators have moved on to a new protocol. The Committee noted that by virtue of the way these patients are treated, there may be insufficient evidence using current approval mechanisms to support a strong recommendation for funding of these cancer drugs. The Committee also noted that once a submission for funding on the Pharmaceutical Schedule is made, then access via NPPA would not be possible.

9.6.6. The Committee noted that for a number of patients, if research protocols were unavailable because an unfunded drug was a component of the comparative

'standard of care', this could result in the use of the Ministry of Health's (limited) high-cost treatment pool for funding.

9.6.7. The Committee noted that access to treatments for a short period of time, in a research setting has not been successful for other patient groups previously. The Committee noted that access to such trials in adult oncology is difficult, in many instances due to the lack of funding of treatments not funded as part of the trial.

9.7. The Committee noted that they potential solutions could be to 'grandparent' all current paediatric oncology drugs, including CAR T-cell therapy, and rescind Schedule rule 8.1b but retain a permissive NPPA process for paediatric oncology drugs. The Committee noted that alternatively, it could be appropriate to retain the current processes but move to a fixed budget, to alleviate concerns about exponential growth in approvals and costs. The Committee however noted that neither solution for paediatric oncology patients would be equitable compared with current arrangements for other patient groups.

9.8. The Committee noted internationally a study that assessed the use of a fixed budget for cancer in England and Wales (the NHS's Cancer Drugs Fund), which indicated that much of the fixed budget is spent on drugs deemed by NICE to be not cost-effective (Chamberlain et al. British J Cancer. 2014.111:1693-702). The Committee considered that ring-fenced funding is an issue and the evidence from overseas indicates that it would not be an effective means of managing a fixed budget. The Committee also considered that an outside-of-budget appropriation, much like what occurred with the recent funding of cost-effective but high budget cost new hepatitis C treatments, could be necessary to resolve this.

9.9. The Committee noted that rescinding rule 8.1b would be difficult and considered that the risks of doing so without a mitigation strategy would be high (poorer health outcomes for children; concerns raised by the stakeholders such as the news media, Human Rights Commission, Children's Commissioner, Health and Disability Commission with loss of public confidence and health sector expectations). The Committee noted that this has highlighted the already apparent bottleneck in drug funding in New Zealand, specifically the length of time that medicines spend on Pharmac's prioritisation list.

9.10. The Committee considered that this was an extremely complicated issue and that a formal review of this would require significant engagement with clinical and other experts. In addition, the Committee considered that it would be important to engage with consumers, whānau and communities about this issue in order to achieve the best, most equitable outcomes. The Committee considered that it would be important for the Government's independent review of Pharmac to review this particular area during its review of Pharmac and Pharmac processes. The Committee noted the significant service component associated with the treatment of this patient group and considered that it would be useful for Pharmac to involve Te Aho o Te Kahu (The Cancer Control Agency) in these discussions.

10. Micronised progesterone for menopause

Application

10.1. The Committee reviewed the application for the use of micronised progesterone for menopause hormone therapy (previously referred to as hormone replacement therapy).

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 micronised progesterone be listed with a high priority, and with restrictions removed.

10.4. In making this recommendation, the Committee considered the lack of alternative treatments for patients who cannot tolerate currently funded options, the increased risk of breast cancer associated with currently funded options, the health need of women relating to a universal age-related change, and the health need of Māori and Pacific women who are at an increased risk of early menopause. The Committee also considered the unmet health need from low uptake of menopause hormone therapy, as a result of the breast cancer concerns about the currently funded menopause hormone therapy options.

Discussion

10.5. The Committee noted that menopause is the natural cessation of a woman's menstrual cycle and marks the end of fertility and occurs when a woman has not menstruated in 12 consecutive months and can no longer become pregnant naturally. The Committee also noted that menopause can cause uncomfortable and/or debilitating symptoms, such as hot flushes, night sweats, weight gain, and mood fluctuations and that every woman's menopause experience is unique. The Committee noted that menopause is usually age-related as part of a woman's natural life course (unless premature for disease or disease treatment-related reasons) and that menopause symptoms begin in the few years before menopause and can continue for four or more years after menopause.

10.6. The Committee noted that the average age of natural menopause for New Zealand women is stated to be 52 years but can occur anytime between the ages of 45 and 55 years and that the estimated number of women in this age range in New Zealand is approximately 230,000. The Committee noted that 5 -10% of women in the menopausal age range would be taking menopause hormone therapy (MHT).

10.7. The Committee noted that menopause affects women universally, and given the sometimes debilitating nature of its symptoms, any issues with access to effective treatments was a differential gender-based access inequity.

10.8. The Committee noted that micronised progesterone for menopause has been considered multiple times since 2012 by both PTAC and the Endocrinology Subcommittee as follows:

- In May 2012 the Endocrinology Subcommittee was supportive of a listing of micronised progesterone, noting it was the preferred progesterone option
- In August 2012 PTAC recommended the application be declined
- In June 2014 the Endocrinology Subcommittee requested that PTAC reconsider its recommendation to decline
- In November 2014 PTAC accepted the Subcommittees recommendation for re-review in, given new evidence could be presented

- In February 2016 PTAC again recommended the application be declined
- In June 2016 the Endocrinology Subcommittee again requested PTAC reconsider their previous recommendation
- In November 2016 PTAC again reviewed micronised progesterone, where it noted that the only evidence that PTAC had not seen previously cited by the Endocrinology Subcommittee (June 2016) was the Dartois et al. (Int J Cancer 2016;138:2415-27) study, and PTAC requested that this be presented at a future PTAC meeting
- In March 2021 the Endocrinology Subcommittee assessed this application, recommending that access to micronised progesterone for menopause hormone therapy be widened by removing the funding restrictions, with a high priority within the context of treatment of endocrine disease.

10.9. The Committee noted that progesterone in combination with oestrogen is used to treat the symptoms of menopause, and that there are significant health risks in women in with an intact uterus if oestrogen is used unopposed, particularly the increased risk of endometrial cancer. The Committee noted that oestrogen is usually combined with a synthetic form of progesterone, which is associated with its own risks, namely an increase in thromboembolic events and breast cancer.

10.10. The Committee noted that the product being considered for this application is a natural micronised progesterone derived from yams which has all the properties of endogenous progesterone, in particular gestagenic, antiestrogenic, slightly anti-androgenic and anti-aldosterone effects. The Committee noted that micronised progesterone is Medsafe approved and is indicated for adjunctive use with an oestrogen in postmenopausal women with an intact uterus for hormone replacement therapy and that the usual dose is 200 mg per day at bedtime at least 12 to 14 days per month, i.e. on days 15 to 26 of each cycle or in the last 2 weeks of each treatment sequence of oestrogen therapy followed by approximately one week without any replacement therapy.

10.11. The Committee noted that at its 2021 meeting, the Endocrinology Subcommittee considered that micronised progesterone lowers an individual's risk of breast cancer cardiovascular disease, mood fluctuation, stroke, and clotting, compared to currently funded synthetic alternatives. The Committee noted that evidence for the use of micronised progesterone comes primarily from the E3N cohort study of 98,995 women initiated in France in 1990 to investigate the risk factors associated with cancer and other non-communicable diseases (Dartois et al. Int J Cancer 2016;138:2415-27).

The Committee noted that the Dartois et al. study reported post-menopausal breast cancer cases as follows; 108 cases in those taking oral oestrogens only (108/1747 participants; hazard ratio (HR) 1.07; 95% CI 0.92 to 1.23), 296 cases in those taking oral oestrogens with progesterone/dydrogesterone (296/4621 participants; HR 1.20; 95% CI 1.09 to 1.32), and 412 cases in those taking oral oestrogens with other progestogen (412/5253 participants; HR 1.72; 95% CI 1.57 to 1.88).

10.12. The Committee was made aware of a systematic review and meta-analysis comparing progesterone with synthetic progestins, each in combination with oestrogens, against the risk of breast cancer and cardiovascular events (Asi et al.

Syst Rev. 2016;5:121). The Committee noted that this study did not include the Dartois et al. study, and that it reported that progesterone was associated with lower breast cancer risk compared with synthetic progestins when each is given in combination with oestrogen (relative risk 0.67; 95 % CI 0.55 to 0.81).

10.13. The Committee noted a systematic literature review on the impact of menopausal hormone therapy (MHT) containing micronised progesterone on the mammary gland (Stute et al. Climacteric. 2018;21:111-22). The Committee noted that the review included 19 studies, with multiple reports from the same authors, including relating to the E3N cohort. The Committee noted that the study reported no increased risk of breast cancer for up to five years with the use of micronised progesterone in combination with oestrogen. The Committee also noted, however, that micronised progesterone or dydrogesterone were associated with a slight but significant increase in breast cancer risk after an average of 6 years of treatment duration.

10.14. The Committee was made aware of a 2020 summary of evidence that stated that it appears that minimal oestrogen is required to initiate the biological processes that promote cancer development (Khan S A. JAMA Netw Open. 2020;3:e203608). The Committee considered that the progesterone effect in breast cancer incidence is minor, but that this depends on the type of cancer.

10.15. The Committee also noted the following evidence relating to the use of micronised progesterone in the management of menopause symptoms:

Yang et al. Gynecol Endocrinol. 2017;33:87-92

Scarabin PY. Climacteric. 2018;21:341-45

Canonico et al. Maturitas. 2011 Dec;70:354-60

Manson et al. JAMA. 2017 Sep 12;318:927-38

Palacios et Mejía. Expert Opin Drug Saf. 2016 Nov;15:1515-25

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause. 2017 Jul;24:728-53

Baber et al. Climacteric. 2016 Apr;19:109-50

Warren. Climacteric. 2018 Aug;21:355-357

International Menopause Society Webinar. March 23 2021

Gompel. Climacteric. 2012 Apr;15 Suppl 1:18-25

Cordina-Duverger et al. PLoS One. 2013 Nov 1;8:e78016

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Menopause. 2017;24:728-53

10.16. The Committee considered that the evidence suggests that the risk of venous thromboembolism increases by about one half with synthetic progesterone, and that synthetic progesterone has an androgenic effect which increases cardiovascular risk. The Committee noted that micronised progesterone does not have this androgenic activity and thus might be expected to not increase cardiovascular risk. The Committee also noted that in France studies have been published widely on the use

of micronised progesterone reducing side effects such as bloating, mood swings, depression and acne. The Committee noted that the increased risk of breast cancer from existing MHT treatments persists for more than 10 years following discontinuation of treatment, and that those women who used MHT for 10 years had double the chance of developing breast cancer than those who used it for only 5 years (Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 2019;394:1159-68).

10.17. The Committee noted that risks relating to endometrial cancer were not discussed at the 2021 Endocrinology Subcommittee meeting. The Committee noted a publication investigating the risk of endometrial cancer associated with different hormone replacement therapies in the E3N cohort (Fournier et al. Am J Epidemiol. 2014;180:508-17). The Committee noted that 301 endometrial cancers were reported in total, and that the use of micronised progesterone with oestrogen increased the risk of endometrial cancer compared with those who had never used MHT (hazard ratio 1.80; 95% CI 1.38 to 2.34). The Committee also noted that the risk increased with prolonged use; those using micronised progesterone for less than five years had a hazard ratio of 1.30, which increased to 2.66 with use spanning longer than 5 years. The Committee noted, however, that the dose of micronised progesterone in the study was unclear and that many of the patients used micronised progesterone as a vaginal gel. The Committee considered that the dose of micronised progesterone may not have been high enough to mitigate the effect of oestrogen in inducing endometrial cancer.

10.18. The Committee was made aware of a 3-year multicentre, randomized, double-masked, placebo-controlled trial investigating the risk of endometrial hyperplasia in 596 postmenopausal women aged 45 through 64 years without contraindication to hormone therapy who were randomised to receive either placebo, conjugated equine oestrogens, conjugated equine oestrogens with medroxyprogesterone acetate, or conjugated equine oestrogens with micronised progesterone (Judd et al. JAMA. 1996;275:370-5). The Committee noted that patients receiving oestrogens in combination with progesterone did not have an increased rates of endometrial hyperplasia compared to placebo (P=0.16). The Committee considered that pharmacoepidemiology studies are a more reliable source of information regarding development of rare adverse events over time than randomised controlled trials.

10.19. The Committee were made aware of a study investigating the association of various types of hormone therapies with the risk of endometrial cancer among postmenopausal women recruited into the European Prospective Investigation into Cancer and Nutrition between 1992 and 2000 (Allen et al. Am J Epidemiol. 2010:172:1394-403). The Committee noted that of 115,474 women in the study, 601 developed endometrial cancer, and that 81% of these cases were verified. The Committee noted that the hazard ratio associated with micronised progesterone was 2.42, compared with 1.73 with synthetic progesterone (95% CIs 1.53 to 3.38 and 0.84 to 1.97, respectively). The Committee considered that this study had a low risk of selection bias, a moderate risk detection bias, high internal validity, and was of moderate quality.

10.20. The Committee noted a systematic review of progesterone and endometrial cancer which included 11 randomised controlled trials and 14 observational studies (Sjögren et al. Maturitas. 2016;91:25-35). The Committee noted that micronised progesterone increased the risk of endometrial cancer, especially when used continuously (former use of micronised progesterone was associated with a hazard ratio of 1.44 [95% CI 0.99 to 2.08] compared with 2.42 with 'current use' [95% CI 1.53

to 3.83]). The Committee noted that other types of progesterone did not seem to affect the risk of endometrial cancer.

10.21. The Committee noted a systematic review of MHT and the risk of endometrial cancer that included 31 papers, only two of which were randomised controlled trials, and also included the Sjogren et al. and Allen et al. papers (Tempfer et al. Cancers (Basel). 2020;12:2195). The Committee noted that short term use of micronised progesterone (5 years or less) was not associated with an increased risk of endometrial cancer. The Committee noted that the randomised controlled trials in this review did not adjust for confounders and were of low precision, and that some of the studies included were funded by drug manufacturers. The Committee also noted that very few studies excluded the possibility of cancer hyperplasia at enrolment, and that the majority of participants in the studies self-reported exposure to the study drugs, which carries the risk of detection and recall bias. The Committee considered that studies with a single baseline exposure categorisation carry a classification bias, as some women may have used different hormone formulations.

10.22. The Committee was made aware of a study investigating the ethnic-specific trends in endometrial cancer across different age groups in New Zealand (Scott et al. Cancer Causes Control. 2019;30:121-27). The Committee noted that there has been a gradual increase in endometrial cancer registrations in New Zealand since 1996, and that Pacific women have the highest registered incidence.

10.23. The Committee noted that body mass index (BMI) is a strong indicator of endometrial cancer risk and that the association is no longer clear among users of MHT (McCullough et al. Cancer Epidemiol Biomarkers Prev. 2008;17:73-9). The Committee noted that use of MHT has been associated a reduced risk of endometrial cancer due to being high BMI/obesity, and that this association does not differ between continuous and sequential therapy (Crosbie et al. Cancer Epidemiol Biomarkers Prev. 2010;19:3119-30). The Committee also noted that in a large US cohort study that those with a BMI of over 30 had a relative risk of developing endometrial cancer of 5.41 compared to those with a BMI under 25 in those who had never used MHT, compared to a relative risk of 2.35 amongst those who had formerly used MHT (Chang et al. Cancer Epidemiol Biomarkers Prev. 2007;16:723-30). The Committee noted that progestagens are considered to potentially counteract the adverse effect of oestrogens on the endometrium, that association between progestagen use and endometrial cancer risk being greater the more days every month that progestagens are added to oestrogen and the more obese that users are (Beral et al. Lancet. 2005;365:1543-51).

10.24. The Committee considered that the evidence suggests that currently funded MHTs carry an increased risk of breast cancer, though the evidence is mixed, and that the effect of MHT on breast cancer is likely to differ according to the type of breast cancer. The Committee considered that if there is an increased risk of breast cancer, that it is likely the risk increases with duration of treatment and persists after discontinuing treatment. The Committee considered that micronised progesterone may also carry an increased risk of breast cancer (compared to non-users of MHT) but the extent of this increased risk was marginal, and micronised progesterone was probably associated with lower risks when compared with synthetic progesterone. However, the Committee considered the lack of published evidence reporting mortality benefits of micronised progesterone limited conclusions about differences in breast cancer risk.

10.25. The Committee considered that overall, micronised progesterone carries an increased risk of endometrial cancer and breast cancer, although the breast cancer

risk associated with micronised progesterone is lower than with other MHT therapies. The Committee noted that breast cancer incidence in New Zealand is much higher than endometrial cancer, and considered that any decrease in breast cancer incidence would be beneficial for patients and the health system and thus any relative reduction in breast cancer incidence would outweigh a potential increase in endometrial cancer. The Committee considered that there was no evidence to indicate if the increased risk of endometrial cancer persists beyond treatment discontinuation. The Committee considered that the increased endometrial cancer risk may also be manageable in many cases if patients present with low grade endometrial cancer, as this can be resolved through withdrawal of the agent.

10.26. The Committee considered that while there was uncertainty in the magnitude of difference in breast cancer risk between agents, it was likely that micronised progesterone may be associated with an improved side effect profile vs synthetic progesterone. The Committee considered that it was unlikely micronised progesterone was superior with regard to mood fluctuations vs currently funded MHTs.

10.27. The Committee noted a recent UK study which reported 14 million workdays lost annually by women suffering from symptoms of menopause, and that 25% of women going through menopause consider leaving work due to their symptoms (Burness Paul report: Menopause in the Workplace. 2019). The Committee considered that it is important to have options for patients who cannot tolerate the currently available funded options.

10.28. The Committee considered that if micronised progesterone were to be funded for this indication nearly half of women would switch to this from synthetic progesterone, and that women who do not take MHT due to the breast cancer risk, may be more likely to start treatment if micronised progesterone were available. The Committee also considered that it is likely that all women initiating MHT would start on micronised progesterone. The Committee noted that uptake of MHT in the Māori and Pacific community is low and considered that a different treatment option may increase use in these communities. The Committee noted, however, that the reason for the decreased up take in these communities is likely attributable to a variety of factors, including perceived safety concerns, intolerance issues and access inequities, and that the lower uptake is unlikely to be purely a function of insufficient treatment options. The Committee considered that uptake may also be higher than predicted due to micronised progesterone being 'natural' and the perceived and actual benefits of this over synthetic progesterone.

10.29. The Committee considered that MHT uptake has been reducing over time, and this may be due to the perceived safety concerns around MHT treatment. The Committee considered that funding a new option that is not perceived to carry the same risks of breast cancer could help improve uptake of MHT. The Committee considered that improved uptake of MHT would improve quality of life and may be associated with fewer women having severe symptoms that force them to stop paid work.

10.30. The Committee considered that the number of additional women who may access MHT (and are not currently receiving MHT) if micronised progesterone were funded is uncertain. The Committee noted that uptake of MHT is much lower in New Zealand compared to overseas and considered that attitudes towards MHT are significantly different overseas and thus difficult to compare to New Zealand. The Committee estimated that it may be reasonable to assume an increase in the number of MHT-treated patients of up to 20% and considered that there is unlikely to be a

large pool of patients not receiving treatment who will switch to micronised progesterone.

10.31. The Committee noted that micronised progesterone is currently listed for the prevention of pre-term labour, and that it is also used in other countries for amenorrhoea and assisted reproductive technology. The Committee considered that if micronised progesterone were to be open listed that it would be used more widely for indications other than MHT for menopause, but that the increase in uptake from these other groups could not be predicted accurately. The Committee considered that the usage in these other indications would likely be small in comparison to the usage in managing menopausal symptoms.

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

Population	Menopausal patients requiring menopause hormone therapy (MHT) A small number of patients accessing micronised progesterone for other indications if listed without restriction
Intervention	Micronised progesterone, dosing either: - 100mg/day on days 1-25 each month, or - 200mg/day on days 15-26 each month Mean duration of use 4.2 years, with ~44% requiring >5 years of treatment (Fournier et al. Am J Epidemiol 2014;180: 508-17)
Comparator(s) (NZ context)	Currently funded MHTs; most commonly prescribed include medroxyprogesterone acetate, oestradiol with norethisterone (which is partially funded), oestradiol valerate and ethinyloestradiol
Outcome(s)	- Improved quality of life compared to patients on no treatment - Efficacy similar to other MHTs in managing menopausal symptoms - Improved side effect profile vs currently funded MHTs - Marginally lower risk of breast cancer compared with currently funded MHTs - Marginally higher risk of breast cancer compared with no treatment, for those patients on treatment for >5 years (Fournier et al. Breast Cancer Res Treat 2014;145: 535-43) - Higher risk of endometrial cancer vs no treatment and vs currently funded MHTs (Fournier et al. 2014) - Lower risk of VTEs vs currently funded MHTs (Huerta et al. Arch Intern 2007;167: 935-43)
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. Aprepitant widening access for nausea and vomiting associated with carboplatin-based chemotherapy

Application

11.1. The Committee considered a clinician application for widened access of aprepitant for nausea and vomiting associated with carboplatin-based chemotherapy.

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 access to aprepitant for nausea and vomiting associated with carboplatin chemotherapy be widened with a **high priority** subject to the following Special Authority criteria (additions in **bold)**:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months where the patient is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy, **and/or carboplatin-based chemotherapy** for the treatment of malignancy.
>
> **Renewal** from any relevant practitioner. Approvals valid for 12 months where the patient is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy, **and/or carboplatin-based chemotherapy** for the treatment of malignancy

11.4. In making these recommendations the Committee considered the high health need of patients experiencing nausea and vomiting associated with carboplatin-based chemotherapy and evidence of benefit of aprepitant in the reduction in nausea and vomiting in this patient population with potential reductions in nausea and vomiting associated hospital admissions, improved adherence to carboplatin-based chemotherapy, and the suitability of aprepitant therapy as an oral treatment.

11.5. The Committee **recommended** that aprepitant for nausea and vomiting associated with any moderately emetogenic chemotherapy be **deferred** pending further advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) on the evidence supporting benefit in this wider population, identification of patients most likely to benefit, and if it is more appropriate to use as a first- or second-line treatment.

Discussion

11.6. The Committee noted that aprepitant is currently funded for the treatment of nausea and vomiting associated with highly emetogenic chemotherapies and/or anthracycline-based chemotherapy. The Committee noted that the application requests widening of access to patients undergoing carboplatin-based chemotherapy, which is typically considered a moderately emetogenic chemotherapy. It was noted that advice was also sought on the appropriateness of widening access to patients experiencing nausea and vomiting as a result of any moderately emetogenic chemotherapy regime.

11.7. The Committee noted that it had previously considered aprepitant for post-operative nausea and vomiting, where it recommended funding with a low priority (February 2014 and February 2015) and noted that Analgesic Subcommittee reviewed this in December 2014, where it was recommended for funding with a high priority. The Committee noted it had not previously considered aprepitant for use in carboplatin -based chemotherapy.

11.8. The Committee noted that aprepitant is a neurokinin-1 (NK1) antagonist which blocks signals from NK1 receptors, decreasing the likelihood of nausea and vomiting. The Committee noted that it has not reviewed any other applications for NK1 antagonists, and that no other NK1 antagonist agents are currently funded in New

Zealand with existing treatments targeting dopamine and serotonin receptors. The Committee noted that aprepitant is Medsafe approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (which would include carboplatin) and highly emetogenic cancer chemotherapy.

11.9. The Committee noted that highly emetogenic chemotherapies are therapies that have a 90% or greater frequency of nausea or vomiting, while moderately emetogenic chemotherapies have a 30% to 90% risk of nausea and vomiting. The Committee considered that historically emesis and nausea have not been recorded well, and an individual patient's risk of experiencing emesis or nausea can be difficult to predict, but that treatment of gynaecological cancers is considered to be associated with increased emesis. The Committee noted that the emetogenicity of carboplatin-based chemotherapy is technically in the moderate range of 30% to 90% but considered that carboplatin falls in the higher end of this category and can be considered more emetogenic than other 'moderate' emetogenic chemotherapies.

11.10. The Committee noted that for highly emetogenic therapies, American Society for Clinical Oncology (ASCO) 2020 guidelines recommend a four-drug antiemetic combination including an NK1 antagonist, a 5-hydroxytryptamine3 (5-HT3) receptor antagonist, plus dexamethasone and olanzapine, and that for moderately emetogenic carboplatin-based chemotherapies the recommended antiemetic treatment is a combination of an NK1 antagonist, 5-HT3 antagonist, and dexamethasone (ASCO Guidelines. Hesketh et al. J Clin Oncol. 2020;38:2782-97). The Committee noted that for moderately emetogenic chemotherapies that are not carboplatin-based, a combination of a 5-HT3 antagonist and dexamethasone (without a NK1 antagonist) is recommended. The Committee also noted that European Society for Medical Oncology (ESMO) clinical practice guidelines recommend a combination of an NK1 receptor antagonist, dexamethasone and a 5-HT3 receptor antagonist (Roila et al. Ann Oncol. 2016;27:v119-33).

11.11. The Committee noted that carboplatin-based chemotherapy is used to treat a range of malignancies, including lung, ovarian, gastrointestinal, and uterine cancers, and that approximately 1,900 patients receive carboplatin annually.

11.12. The Committee noted that cancer and the associated treatment side-effects such as nausea and vomiting is often very distressing for family, whānau and caregivers of those affected as well as patients experiencing significant nausea and vomiting as a result of treatment and considered nausea and vomiting associated with carboplatin-based chemotherapy may be a barrier to cancer treatment adherence and perseverance for some patients, which may in turn exacerbate the likelihood of poorer treatment outcomes for patients, and can lead to escalation of cancer therapy to a different agent, which may be associated with an increase in toxicity and/or cost. The Committee noted that there are different phases of nausea and vomiting associated with chemotherapy; the acute phase occurring within the first 24 hours, and a delayed phase typically occurring >24 hours following administration of chemotherapy. The Committee noted that some patients experience anticipatory nausea and vomiting prior to a cycle of chemotherapy, particularly if they experienced nausea and vomiting in previous cycles.

11.13. The Committee noted that Māori and Pacific patients are overrepresented in lung and breast cancers, with these cancers often treated with carboplatin-based chemotherapy.

11.14. The Committee considered that within New Zealand, the anti-emetic treatment regimen used for treatment or prevention of nausea and vomiting associated with carboplatin-based chemotherapy is 8-12 mg dexamethasone on day 1 and 8 mg on days 2 and 3 after treatment, alongside 8-16 mg ondansetron one hour prior to chemotherapy.

11.15. The Committee noted that aprepitant has a long duration of central activity, meaning that it impacts both the acute and delayed phase of emesis following chemotherapy treatment. The Committee noted that, as a CYP inhibitor, aprepitant augments the activity of 5-HT3 antagonists (ondansetron) and dexamethasone, increasing their effect against emesis and nausea.

The Committee noted that the recommended dose of aprepitant is one dose of 125 mg immediately prior to chemotherapy, and 80 mg once daily for the two days following chemotherapy, and that this would be in addition to existing treatments of dexamethasone prior to and post chemotherapy, and ondansetron administered prior to chemotherapy.

11.16. The Committee noted incidentally that the benefits of aprepitant on nausea and vomiting have been reported in patients treated with cisplatin, and noted a multicenter, randomised, double-blind, placebo-controlled phase III study performed to establish the superiority of the aprepitant regimen versus standard therapy in the prevention of chemotherapy-induced nausea and vomiting (Hesketh et al. J Clin Oncol. 2003;21:41112-9). The Committee noted that the proportion of patients not experiencing emesis was higher in the aprepitant treated group in both the acute and delayed phases. The Committee considered that evidence relating to carboplatin-based chemotherapy is more relevant to this application.

11.17. The Committee noted various studies evaluating the use of aprepitant in the treatment of emesis and nausea in patients treated with carboplatin-based chemotherapy:

Suzuki et al. Med Oncol. 2016;33:65: Chemotherapy naïve patients with advanced non-small cell lung cancer (n=63) receiving carboplatin-based chemotherapy were treated with doublet antiemetic therapy with dexamethasone and a 5-HT3 receptor antagonist during the first cycle of chemotherapy, with aprepitant added during the second cycle of chemotherapy.

The Committee noted that the response rate in the acute phase of the first cycle was 98.4% (95% CI 91.5% to 100.0%) and 93.7% in the second cycle (95% CI 84.5% to 98.2%; P=0.250). The Committee also noted that the complete response rates in the delayed phase were 66.7% in the first cycle (95% CI 53.7% to 78.0%) and 90.5% in the second cycle (95% CI 80.4% to 96.4%; P<0.001). The Committee noted the overall complete response rate was significantly improved in the second cycle (87.3%) compared with the first cycle (65.1%; p<0.001).

The Committee noted that aprepitant increases the concentration of dexamethasone, and the dose of dexamethasone was therefore reduced in the second cycle.

Yahata et al. Int J Clin Oncol. 2016;21:491-7: a multicentre placebo-controlled, double-blind, randomised study of 324 patients with gynaecologic cancer who were naïve to paclitaxel and carboplatin and who were treated with a paclitaxel and carboplatin combination chemotherapy regimen of paclitaxel and carboplatin

every 3 weeks. The Committee noted patients were randomised to receive either aprepitant or placebo in combination with ondansetron/granisetron (5-HT3 antagonist) and dexamethasone.

The Committee noted, in the acute phase, the proportion of patients with 'no vomiting' was 96.0% in the aprepitant treated group versus 91.1% of patients in the placebo treated group (p = 0.0495). In the delayed phase 80.1% of patients in the aprepitant group versus 56.9% of patients in the placebo group placebo (p< 0.0001) experienced no vomiting.

The Committee noted, in the acute phase, the proportion of patients with 'no significant nausea' showed no significant difference between groups, but the delayed phase showed a response of 85.4% in the aprepitant group versus 76.0% in the placebo group (p = 0.0274). The Committee noted experiencing 'no nausea' generally was different between groups in either phase.

11.18. The Committee also noted the following studies relating to the use of aprepitant in the reduction of nausea and vomiting associated with carboplatin-based chemotherapy:

Jordan et al. Bone Marrow Transplant. 2011;46:784-9

Maehara et al. Anticancer Res. 2015;35:5427-34

Kusagaya et al. Lung Cancer. 2015'90:410-6

Ito et al. Lung Cancer. 2014;84:259-64

Tanioka et al. BR J Cancer. 2013;109:859-65

Fujiwara et al. J Gynecol Oncol. 2015;26:311-9

Choi et al. Support Care Cancer. 2014;22:1181-7

Kitazaki et al. Support Care Cancer. 2015;23:185-90

Jordan et al. Support Care Cancer. 2016;24:4617-25

11.19. The Committee noted a meta-analysis of randomised trials comparing NK1 receptor antagonist (aprepitant in all but one trial) with dexamethasone and a 5-HT3 receptor antagonist (ondansetron or granisetron) versus dexamethasone with 5-HT3 receptor antagonist in patients receiving the first cycle of carboplatin-based chemotherapy (Di Maio et al. Crit Rev Oncol Hematol. 2018;124:21-8).

The Committee noted that in the acute phase, the complete response rate was significantly higher with addition of NK1 receptor antagonist, with a response rate of 94.5% versus 90.1% (odds ratio (OR) 1.75, 95% CI 1.19 to 2.59, p=0.005). The Committee noted that in the delayed phase, the complete response rate was significantly higher with addition of NK1 antagonist with a response rate of 76.4% versus 61.7% (OR 2.04, 95% CI 1.64 to 2.55, p<0.00001). The Committee also noted that in the overall period (0-120 hours), the complete response rate was significantly higher with the addition of NK1 RA: 75.3% versus 60.4% (OR 2.04, 95%CI 1.64-2.54, p<0.00001).

11.20. The Committee considered that the strength and quality of evidence for aprepitant in the treatment of nausea and vomiting associated with carboplatin-based chemotherapy to be moderate.

11.21. The Committee considered aprepitant use for treatment of nausea and vomiting associated with carboplatin-based chemotherapy would not be replacing any currently available treatments and would be used in addition to current treatments. The Committee considered that while this may incur additional pharmaceutical costs, there are likely to be some savings from reduction in hospital re-admissions and/or treatment of emesis; however, the Committee considered it unlikely that treatment would reduce the length of initial hospital stay associated with chemotherapy administration. The Committee considered that treatment with aprepitant is likely to improve adherence to chemotherapy treatment and may improve uptake of chemotherapy in patients who are anxious about nausea and vomiting. The Committee noted that clinical trials have not demonstrated a significant reduction in treatment adherence associated with aprepitant use, or discontinuation in those treated with placebo, but considered that this may not be representative of a real-world situation.

11.22. The Committee noted that although carboplatin-based chemotherapy is not formally considered to be 'highly emetic, many clinicians consider it to be, and considered that the fiscal impact of funding aprepitant for this indication would be small considering the number of patients already receiving this treatment. The Committee noted that CADTH in Canada has recommended that aprepitant be added to antiemetic treatment in the second chemotherapy cycle if nausea and vomiting are significant with highly emetogenic chemotherapies. The Committee also noted that it was unclear if aprepitant use would be more appropriate as a first- or second-line treatment, and that advice should be sought from CaTSoP regarding this.

11.23. The Committee considered that if aprepitant were funded for carboplatin-based chemotherapy that this would quickly become standard of care and would likely be used in treatment naïve patients prior to their first chemotherapy cycle. The Committee considered that uptake would be close to 100%.

11.24. The Committee considered that there may be some benefit in widening access to allow all patients treated with moderately emetogenic chemotherapy to access aprepitant but noted that there is no evidence for this, that international guidelines do not include this in their recommendations, and that even though carboplatin is considered to be moderately emetogenic, it has been singled out as requiring extra anti-emetic treatment by some clinicians and is considered to be a highly emetogenic therapy compared to other moderately emetogenic therapies. The Committee considered that further advice from CaTSoP should be sought on cancer patient populations that would benefit from access to aprepitant.

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

Population	Patients receiving carboplatin-based chemotherapy
Intervention	Aprepitant 125mg prior to chemotherapy (day 1); 80mg on days 2 and 3 post chemotherapy. To be administered in addition to the current antiemetic treatments, alongside chemotherapy, i.e. triplet antiemetic therapy.
Comparator(s) (NZ context)	Dexamethasone 8-12 mg pre-chemotherapy (day 1); 8mg on 2 and 3 after treatment, and ondansetron 8-16 mg one hour prior to chemotherapy, alongside chemotherapy.
Outcome(s)	Reduced frequency and/or intensity of vomiting and nausea in the acute (0-24 hr) and delayed phase (24-120 hr) following chemotherapy.
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. Erenumab for the prophylactic treatment of migraine

Application

12.1. The Committee reviewed applications for erenumab:

- A consumer application for migraine in adults who have at least four migraine days per month
- A consumer application for chronic and acute migraine
- Supporting information from the supplier of erenumab
- Supporting information from neurologists.

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 erenumab for the treatment of migraine be funded with a **low priority**, subject to the following Special Authority criteria:

ERENUMAB
Initial application from a relevant practitioner. Approval valid for 3 months.
All of the following:
1. Patient has chronic migraine defined as experiencing at least 15 headache days per month (with at least 8 days having headache with migraine features), for at least 3 months; and
2. Patient's migraines are refractory to at least three funded prophylactic agents; and

Renewal from a relevant practitioner. Approval valid for 6 months.
1. Improvement in number of migraine days per month of at least 50% compared with baseline.

In making this recommendation the Committee considered:

- the health need of patients with migraine who have trialled three treatments without adequate response
- the evidence of moderate quality and strength for a benefit from erenumab for migraine, with the 140 mg dose providing better duration of effect and long-term outcomes than 70 mg

- the high cost of erenumab and uncertainty regarding savings to the health sector
- the impact of funding erenumab on primary and secondary care services
- the risk that funding erenumab could lead to an increase in the existing health inequities for migraine treatment.

12.4. The Committee considered that Pharmac could seek further advice regarding the application for erenumab for migraine from the Neurology Subcommittee, including: where erenumab would be placed in the sequence of migraine treatment; the need for secondary care advice in this patient population; costs of subcutaneous administration and training; and the proposed Special Authority criteria.

12.5. The Committee considered that Pharmac could seek further advice from the Analgesics Subcommittee regarding the application for erenumab for migraine , the needs of patients with chronic headache, and the treatment paradigm for patients with chronic headache.

Discussion

12.6. The Committee noted that migraine is a debilitating neurological disease characterised by severe throbbing head pain lasting for several hours or up to a few days, which may be associated with vision changes, sensitivity to light, nausea, vomiting, forgetfulness and weakness. The Committee noted that migraine can severely impact a person's quality of life, ability to care for themselves and their family, work and productivity, as well as having an emotional and social impact. The Committee noted that migraine is considered one of the most common global causes of disease-related disability, and considered that the health utility range (0.466) used by the National institute for Health and Care Excellence (NICE) in its Technology appraisal guidance TA682 was reasonable for chronic migraine.

12.7. The Committee noted that activation of the trigeminal nerve is implicated in migraine, as it releases the pro-inflammatory calcitonin gene-related peptide (CGRP) which is found at increased levels in people with migraine. The Committee noted that migraine is defined as either episodic, with headache occurring on less than 15 days per month, or chronic, where there are at least 15 headache days per month of which at least 8 have migraine features. The Committee noted that there are overlapping symptoms between chronic migraine and chronic tension-type headache, analgesic overuse headache, stress headache, and chronic headache that may make the diagnosis of migraine difficult. The Committee noted that people with chronic headache may require a holistic, psychosocial approach from pain services.

12.8. The Committee noted that the prevalence of chronic migraine has been reported to be between 1.4% and 2.2%, although approximately 8.1% of the adult population in Australia is diagnosed with migraine (Natoli et al. Cephalalgia. 2010;30:599-609). The Committee noted that migraine prevalence (including tension-type headache) in New Zealand was reported to be about 17% of the 2016 population by a systematic analysis of migraine and tension-type headache for the Global Burden of Disease Study 2016 (GBD 2016 Headache Collaborators. Lancet Neurol. 2018;17:954-976), however this overestimated the size of the migraine population by including tension-type headache. The Committee considered that it was reasonable to estimate migraine prevalence of 1.8% in New Zealand, noting that there is poor data for the prevalence of migraine in New Zealand and to inform whether there is any

difference in prevalence between Māori, Pacific peoples or non-Māori and non-Pacific populations.

12.9. The Committee noted that most people with migraine are managed in primary care (some access treatment via private secondary specialists) and that a range of funded treatments are available for migraine. The Committee noted that propranolol, amitriptyline and topiramate may be used for either episodic or chronic migraine; pizotifen and sodium valproate may be used for episodic migraine; and botulinum toxin injections may be used for chronic migraine.

12.10. The Committee noted that despite referral, access to neurology specialists, particularly for people with migraines in the public health system is currently limited due to high demand for neurology services and that it may be even more difficult for patients living at a distance from secondary care e.g. in rural locations. The Committee noted that botulinum toxin injections for migraine would be administered within neurology services and considered that botulinum toxin is not currently an accessible treatment option for most people with migraine who are treated in the public sector. The Committee noted that botulinum toxin injections are used in private care, resulting in access inequities for those who are not able to access private treatment. The Committee therefore considered that botulinum toxin was not an appropriate comparator to erenumab in New Zealand.

12.11. The Committee considered that patients who have tried at least three prophylactic anti-migraine medicines but still experience migraines have an unmet health need. The Committee considered that it was reasonable to assume approximately 28% of patients with migraine take migraine prophylaxis (based on Bloudek et al.J Headache Pain. 2012;13:361-78) and that 9% would have trialled at least three funded therapies but found these to be ineffective (based on the NICE Technology appraisal guidance TA682). The Committee considered that many patients with migraine also experience medicines overuse, either using analgesics for more than 15 days per month or opioids (which is known to occur internationally) or triptans for more than 10 days per month.

12.12. The Committee noted that erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody that reversibly binds to the CGRP receptor, modifying the trigeminal nerve signalling. Members noted that erenumab is thought to prevent migraine (which occurs within the blood-brain barrier) via CGRP blockade, although erenumab does not cross the blood-brain barrier. The Committee noted that erenumab is a medicine that has not previously been considered by Pharmac for any indication. The Committee noted that Medsafe has approved erenumab 70 mg and 140 mg for prophylaxis of migraine in adults, administered subcutaneously every four weeks. The Committee noted that erenumab is presented as 70 mg vials and that a dose of 140 mg requires two injections.

12.13. The Committee noted evidence from Liberty; a randomised (1:1), phase IIIb, double-blind, placebo-controlled study of 246 adult patients with episodic migraine experiencing 4-14 migraine days per month (mean 9.3 at baseline) for the past three months, treated unsuccessfully with 2-4 migraine treatments, who received either erenumab 140 mg or placebo every four weeks for 12 weeks (Reuter et al. Lancet. 2018;392:2280-7). The Committee noted that the primary endpoint of Liberty was the proportion of patients achieving ≥50% reduction in the mean number of monthly migraine days during weeks 9-12, and that at week 12, this was reported in 30% of those taking erenumab compared with 14% of those taking placebo (odds ratio 2.7; 95% CI 0.4 to 5.2; *P*=0.002).

12.14. The Committee noted evidence from Study 295; a randomised (3:2:2), phase 2, double-blind, placebo-controlled, multicentre study of 667 adults aged 18 to 65 years with chronic migraine (defined as 15 or more headache days per month, of which eight or more were migraine days) who received either erenumab 70 mg, erenumab 140 mg or placebo subcutaneously every four weeks for 12 weeks (Tepper et al. Lancet Neurol. 2017;16:425-34). The Committee noted that Study 295 participants had a mean of about 18 migraine days (and 20 headache days) per month at baseline. The Committee noted that the study excluded those who had trialled more than three medications for prophylactic treatment of migraine and considered that the trial population was not the exact group considered to have a health need for a new agent such as erenumab in New Zealand. The Committee noted that the primary endpoint of Study 295 was the change in monthly migraine days from baseline to the last four weeks of double-blind treatment (weeks 9−12), which was reported to be −6.6 days with both erenumab 70 mg and 140 mg vs −4.2 days with placebo; a difference of −2.5, (95% CI −3.5 to −1.4, *P*<0.0001). Members considered this active difference was a small reduction in the context of severe migraines. The Committee noted that anti-erenumab antibodies were reported in 11 patients in the 70 mg group and three in the 140 mg group in Study 295, none of which were neutralising.

12.15. The Committee noted further evidence from Liberty including a three-year open-label extension (Goadsby et al. Neurology. 2021;96:e2724-e35), and further evidence from Study 295 including a 52-week open-label extension (Tepper et al. Cephalalgia. 2020;40:543-53) and patient-reported outcomes (Lipton et al. Neurology. 2019 ;92:e2250-e2260). The Committee noted there was a large amount of placebo-controlled clinical trial evidence for the use of erenumab for the treatment of migraine, including the following:

- Goadsby et al. N Engl J Med. 2017;37:2123-32
- Goadsby et al. Neurology. 2020;95:e469-e79
- Dodick et al. Cephalalgia. 2018;38:1026-37
- Ashina et al. Eur J Neurol. 2021;28:1716-25

12.16. The Committee considered that this placebo-controlled trial evidence indicates that erenumab has an effect, although placebo responses were noted therefore the difference in effect between active treatment and placebo was of a lesser magnitude. Members considered that the placebo responses were not unexpected in this population with pain from chronic migraine. The Committee considered that the evidence from Study 295, in particular, suggested there is a proportional dose response curve for erenumab and that while it provides some short-term benefit at both the 70 mg and 140 mg doses with similar efficacy and toxicities, the 140 mg dose provides better duration of effect and long-term outcomes than the 70 mg dose.

12.17. The Committee was made aware of evidence from a non-interventional, retrospective, exploratory, claims database analysis of treatment effectiveness (Tepper et al. J Manag Care Spec Pharm. 2021;27:1157-70). Members considered that this provided poor quality data of fewer claims on average for acute migraine treatments in patients who received erenumab compared with patients who received botulinum toxin. However, the Committee noted there was no difference in claims for acute migraine treatments when compared with patients who received triptans or barbiturates.

12.18. The Committee noted that there was no head-to-head, randomised controlled trial evidence for erenumab compared with botulinum toxin, other anti-migraine therapies or other monoclonal antibodies. The Committee noted that the clinical trial data did not provide outcomes beyond 52 weeks, whereas chronic migraine would usually continue beyond one year. The Committee considered that the evidence was of moderate strength and quality, noting that one trial (Study 295) did not include the target population. The Committee noted that there was no clinical trial data for the use of erenumab in New Zealand patients but considered there was no reason to assume any difference in benefits or risks would be seen in the New Zealand population.

12.19. The Committee noted that upper respiratory tract infections were common adverse events associated with erenumab, however, the Committee considered that the safety profile of erenumab overall was less serious than that reported for other monoclonal antibodies that target immune pathways. The Committee noted that post-marketing data reported the incidence of myocardial infarction, pulmonary embolism and hypertension which were events of concern. The Committee noted that the anti-drug antibodies reported with erenumab were transient and non-neutralising.

12.20. The Committee considered that the most appropriate use of erenumab would be for patients with episodic or chronic migraine who have trialled three prophylactic agents previously, although this would require a careful diagnosis given the possibility of differential diagnoses. The Committee considered that, patients with chronic migraine would have a greater health need and may receive greater benefit from funded access to erenumab compared with episodic migraine.

12.21. The Committee considered that patients seeking funded access to erenumab would likely be receiving prophylactic migraine therapy (even if ineffective) which erenumab would replace, and that these patients may use analgesics for breakthrough migraines while on erenumab. The Committee considered that erenumab would be used at a dose of 140 mg in most cases, with patients either starting treatment at this dose or increasing to this dose over time. The Committee considered that erenumab would be used indefinitely unless a patient experienced intolerable adverse events, although members noted that migraine can decrease with age in which case erenumab might be used for approximately 5 to 10 years.

12.22. The Committee considered that, as erenumab is an expensive medicine, it would be reasonable for Pharmac to utilise restrictive funding criteria to target access for erenumab. The Committee considered that an improvement in migraine days of at least 50% compared with baseline was consistent with the clinical trial endpoints and would be appropriate for the purposes of funded treatment renewal, as opposed to a minimal clinically important difference of 30% used by some international jurisdictions.

12.23. The Subcommittee considered that, if erenumab were funded for migraine, there would be significant issues around its prescribing and management across primary and secondary care.

12.23.1. The Committee again noted that access to neurologists in the public health system is currently limited. The Committee considered that a requirement for referral to neurology services for funded access to erenumab e.g. if prescribed by, or on the advice of, a neurologist; would present a barrier to accessing treatment. The Committee considered that the volume of new referrals for migraine, if accepted, would significantly affect neurology services, including their capacity to treat patients with other neurological conditions requiring specialist care.

12.23.2. The Committee considered that from a primary care perspective that, regardless of the level of secondary care support, the effects of having to manage a monoclonal antibody like erenumab could affect that sector's capacity to treat patients with other conditions. Such pressures would be worse if GPs had little specialist secondary care support when starting and maintaining treatment with erenumab, as with any monoclonal antibody. Members considered some GPs would be uncomfortable initiating a patient on erenumab, due to the challenges of accurately diagnosing this specific patient group e.g. the potential overlap with tension-type headache and chronic pain. Members considered that GPs have variable experience and comfort in managing treatment with monoclonal antibodies in practice generally, with many being unfamiliar with these medicines and inexperienced in managing their associated risks.

12.24. The Committee considered that the costs and logistics of erenumab treatment, such as syringe disposal, training for subcutaneous administration, and nursing support were unclear. The Committee considered that syringe disposal by pharmacies or GP clinics may not be feasible therefore disposal requirements and costs, in the absence of a supplier-led disposal programme, may fall on secondary care.

12.25. The Committee considered it was uncertain whether any public health sector savings would result from funding erenumab for migraine e.g. due to a reduction in emergency department presentations or hospitalisations.

12.26. The Committee considered that funding erenumab has the potential to increase the existing inequity of access to this treatment, as it would be easier to access for those who could already obtain it privately while the significant issues around its prescribing and management across primary and secondary care could lead to inequitable access in the public system.

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

Population	Patients with chronic migraine defined as experiencing at least 15 headache days per month (with at least eight days having headache with migraine features), for at least three months; and Patient's migraines are refractory to at least three funded prophylactic agents e.g. propranolol, amitriptyline, topiramate, pizotifen, sodium valproate
Intervention	Erenumab given via subcutaneous injection every four weeks at a dose of 140 mg. Treatment continuation at 12 weeks if patient has had a ≥50% reduction in headache days per month.
Comparator(s) (NZ context)	Current 4th line treatment with recommended prophylactic agents. • Propranolol • Amitriptyline • Topiramate • Pizotifen • Sodium valproate (not for those of childbearing potential)
Outcome(s)	Reduction in the mean number of migraine days per month (≥50% reduction. Reduced days per month requiring acute migraine medication.