Record of the Endocrinology Subcommittee of PTAC Meeting held on 30 March 2021

Endocrinology Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

The Endocrinology Subcommittee 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its August 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

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.

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Attendance

Present

Simon Wynn Thomas (Chair, PTAC member)
Anna Fenton
Andrew Grey
Alistair Gunn
Bruce King *(via zoom)* (PTAC member)
Bruce Small
Esko Wiltshire
Jane Thomas (PTAC member)
Stella Milsom *(part of, via zoom)*

1. Summary of recommendations

1.1. The Subcommittee **recommended** 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.

1.2. The Subcommittee **recommended** that the Special Authority criteria for denosumab for people for whom bisphosphonates are <u>contraindicated</u> be amended with a **high priority**, within the context of treatment of endocrine disease, with the proposed criteria (to replace the current criteria) as follows:

DENOSUMAB
Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. The patient has established osteoporosis; and
2. Any of the following:
    - 2.1. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically and documented bone mineral density (BMD) T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA); or
    - 2.2. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically, and either the patient is 75 years of age or older, or densitometry scanning cannot be performed because of logistical, technical or pathophysiological reasons; or
    - 2.3. History of two significant osteoporotic fractures, as defined by the WHO, demonstrated radiologically; or
    - 2.4. Documented T-score less than or equal to -3.0, measured using DEXA; or
    - 2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements, measured using DEXA; and
3. Either:
    - 3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or
    - 3.2. The patient has experienced at least one symptomatic new fracture or a BMD loss greater than 2% per year, after at least 12 months' continuous therapy with a funded antiresorptive agent.

1.3. The Subcommittee **recommended** that the Special Authority criteria for denosumab for people in whom bisphosphonates are <u>contraindicated, ineffective or not tolerated</u> be amended with a **high priority**, within the context of treatment of endocrine disease, with the proposed criteria (to replace the current criteria) as follows:

DENOSUMAB

Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. The patient has established osteoporosis; and
2. Any of the following:
    - 2.1. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically and documented bone mineral density (BMD) T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA); or
    - 2.2. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically, and either the patient is 75 years of age or older, or densitometry scanning cannot be performed because of logistical, technical or pathophysiological reasons; or
    - 2.3. History of two significant osteoporotic fractures, as defined by the WHO, demonstrated radiologically; or
    - 2.4. Documented T-score less than or equal to -3.0, measured using DEXA; or
    - 2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements, measured using DEXA; and
3. Any of the following:
    - 3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or
    - 3.2. Bisphosphonates are not tolerated due to GI disturbance, severe acute phase reaction or inflammatory ocular disease; or
    - 3.3. The patient has experienced at least two symptomatic new fractures or BMD loss greater than 2% per year; or
    - 3.4. Intravenous bisphosphonates cannot be administered due to logistical or technical reasons.

1.4. The Subcommittee **recommended** that funding restrictions for zoledronic acid be removed with a **high priority** within the context of treatment of endocrine disease.

1.5. The Subcommittee **recommended** the following Special Authority for teriparatide (to replace the current criteria) with a **medium priority**, in the context of treatment of endocrine disease:

TERIPARATIDE
Initial application – from any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:

All of the following:

1. The patient has a documented T-score less than or equal to -3.0, measured using dual energy x-ray absorptiometry; and
2. Either:
    - 2.1 The patient has had two or more fractures due to minimal trauma; or
    - 2.2 The patient has had a clinical vertebral fracture.

1.6. The Subcommittee **recommended** raloxifene be delisted.

1.7. The Subcommittee **recommended** that eplerenone for the treatment of primary aldosteronism for patients intolerant to spironolactone be listed with a **high priority**, within the context of treatment of endocrine disease, subject to the following Special Authority criteria:

EPLERENONE
Initial application – (primary aldosteronism) only from a cardiologist, endocrinologist or nephrologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Both:
1 The patient has had a diagnosis of primary aldosteronism; and
2 Either:

- 2.1. Patient is intolerant to optimal dosing of spironolactone; or
- 2.2. Patient has experienced a clinically significant adverse effect while on optimal dosing of spironolactone.

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Endocrinology Subcommittee 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.

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

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

2.4. The Endocrinology Subcommittee is a Subcommittee of PTAC. The Endocrinology Subcommittee and PTAC and other Subcommittees have complementary roles, expertise, experience, and perspectives. The Endocrinology Subcommittee (and other Subcommittees) may therefore, at times, make recommendations for treatments for endocrine disease that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for endocrine disease that differ from the Endocrinology Subcommittee's, or Subcommittees may make recommendations that differ from other Subcommittees'.

PHARMAC considers the recommendations provided by both the Endocrinology Subcommittee and PTAC and any other relevant Subcommittees when assessing applications for treatments for endocrine disease.

3. Welcome and introduction

3.1. The Subcommittee Chair welcomed members and PHARMAC staff to the meeting. The members and PHARMAC staff in attendance introduced themselves and their roles.

4. Record of previous Endocrinology Subcommittee meetings

4.1. The Subcommittee noted the records of the Endocrinology Subcommittee meetings held on 21 June 2016, 17 May 2018 and 23 November 2020 and agreed that the minutes be accepted.

5. Previous action points/recommendations made

5.1. The Subcommittee noted PHARMAC was currently consulting on a proposal to widen access to octreotide LAR for pre-operative acromegaly. The Subcommittee considered not all clinicians would use octreotide LAR prior to pituitary surgery but there was benefit for some patients where octreotide LAR would shrink the tumour back into the pituitary fossa, assisting surgical treatment. Members were supportive of the proposal and considered the widening of access to octreotide LAR for pre-operative acromegaly would be a high priority for funding, within the context of endocrine treatments.

5.2. The Subcommittee noted the updates on the remaining action points from the last Endocrinology Subcommittee meeting.

6. Correspondence and Matters Arising

6.1. Members of the Subcommittee highlighted concern regarding the brand change for goserelin. The brand change occurred as a result of a competitive process, with the new brand (Goserelin Teva) listed from 1 December 2020 and the 'old' brand (Zoladex) due to be delisted, with Goserelin Teva having Sole Supply Status, from 1 May 2021. Members reported significant patient discomfort with the administration of the new brand due to the injection device and considered that many patients previously stable on treatment may be unwilling to receive further treatment as a result, particularly in older patients.

6.2. The Subcommittee requested PHARMAC staff follow this up with relevant members outside of the meeting.

7. Therapeutic Group and NPPA Review

Update on Funding Decisions

7.1. The Subcommittee noted the update on funding decisions since the last Endocrinology Subcommittee meeting, which included levonorgestrel intrauterine system for heavy menstrual bleeding and endometriosis, somatropin for people with Prader-Willi syndrome under the age of two years and the removal of restrictions on alendronate sodium (with or without colecalciferol).

Outstanding Funding Applications

7.2. The Subcommittee noted the outstanding funding applications.

7.3. The Subcommittee considered there were new systematic reviews for growth hormone treatment (somatropin) in adolescents and adults with Prader-Willi Syndrome (PWS) and considered it would be beneficial to reconsider this application in light of the new evidence, rather than propose to decline these as inactive applications. The Subcommittee considered it unlikely any new evidence would be of higher quality than that previously considered due to small patient numbers. However, the Subcommittee considered there was still a potential health benefit which should be reviewed.

7.4. The Subcommittee considered short children born small for gestational age were a specific patient subgroup which would likely benefit from wider access to growth hormone treatment (somatropin). The Subcommittee considered, on average, these patients have a smaller adolescent growth spurt and therefore standard height prediction curves do not appropriately predict the likely growth of these patients. The Subcommittee considered it would be beneficial to review this application with consideration of this issue.

7.5. The Subcommittee noted PTAC's recommendation for zoledronic acid for use in the prevention of bone loss post spinal cord injury. The Subcommittee considered zoledronic acid could be given every 18 months for this indication. Members were supportive of the proposal and considered the widening of access to zoledronic acid to use in the prevention of bone loss post spinal cord injury would be a high priority for funding, within the context of endocrine treatments.

Therapeutic Group Expenditure Summary

7.6. The Subcommittee noted the expenditure on pharmaceuticals listed under the Hormone Preparations therapeutic group and Drugs Affecting Bone Metabolism therapeutic subgroup and the pharmaceuticals with the highest net expenditure. The Subcommittee noted the impact of COVID-19 on the usage of many treatments within these groups. No specific concerns regarding this impact were raised. No specific comments or concerns regarding the overall expenditure for endocrine treatments were raised.

Calcium Homeostasis

7.7. The Subcommittee noted the information provided regarding pharmaceuticals in the Calcium Homeostasis therapeutic subgroup.

7.8. The Subcommittee considered a preference for a higher strength cinacalcet tablet to reduce the potential pill burden for patients, providing a more suitable treatment option. The Subcommittee considered both the 60 mg and 90 mg tablets would be beneficial given the range in potential cinacalcet dosing for patients. The Subcommittee considered it would be important to maintain the 30 mg tablets, even if another strength tablet were to be listed.

Corticosteroids and Related Agents for Systemic Use

7.9. The Subcommittee noted the information provided regarding pharmaceuticals in the Corticosteroids and Related Agents for Systemic Use therapeutic subgroup.

7.10. The Subcommittee considered there was an unmet health in young children which would be addressed by a 1 mg hydrocortisone tablet. The Subcommittee considered the currently funded hydrocortisone tablets (5 mg and 20 mg) were inappropriate for use in young children given the required dosing in these patients and that these patients would be unlikely to transition to the funded tablets until mid-childhood or later. The Subcommittee noted hydrocortisone tablets are currently compounded into an oral liquid for paediatric patients, and the compounded liquid is unstable (with a seven-day expiry). The Subcommittee considered many of these patients would also require thyroxine and that there would be benefit for clinicians, paediatric patients and their carers if patients could transition to thyroxine and hydrocortisone tablets at the same time. A smaller tablet strength would support this approach.

7.11. The Subcommittee highlighted endocrinologists do not commonly prescribe prednisone, however considered GPs would be well placed to consider a market transition. The Subcommittee noted prednisone is equivalent in its corticosteroid dosing to prednisolone, as noted in the NZF and UpToDate. The Subcommittee considered education to prescribers would be required to support a market transition from prednisone to prednisolone.

7.12. The Subcommittee considered the benefit of maintaining the same range of tablet strengths for prednisolone, including the lower strengths. The Subcommittee considered this would minimise the risk of steroid-related side effects by providing prescribers with dosing flexibility. The Subcommittee considered it important PHARMAC seeks further advice regarding the risks of a market transition.

Sex Hormones Non Contraceptive

7.13. The Subcommittee noted the information provided regarding pharmaceuticals in the Sex Hormones Non Contraceptive therapeutic subgroup.

7.14. The Subcommittee noted the prescriber breakdown for testosterone undecanoate and considered this would not reflect circumstances where patients were started on treatment by a specialist and then continued by a GP.

7.15. The Subcommittee highlighted the benefit of a testosterone gel product. The Subcommittee considered the virilisation risk associated with testosterone gel however considered there is a virilisation risk and potential for abuse across all testosterone products.

7.16. The Subcommittee noted a request for a 10 mg strength cyproterone acetate tablet for testosterone suppression in transgender women who have not had gonad removal. The Subcommittee considered the 50 mg tablet can easily be broken (both in half and into quarters) and there was no unmet health need in this patient group which would be met by a 10 mg strength tablet. The Subcommittee considered that doses of 10 mg of cyproterone acetate are too low to provide anti-androgen effect.

Hormone Replacement Therapy - Systemic

7.17. The Subcommittee noted the information provided regarding pharmaceuticals in the Hormone Replacement Therapy - Systemic therapeutic subgroup.

7.18. The Subcommittee considered a lower-dose oestrogen preparation for paediatric patients would be used if available, however considered this would be a low priority. Members indicated the current 25 mg patches are cut into quarters and administered once or twice a week for paediatric patients. The Subcommittee noted BPAC guidelines started paediatric patients on a 1/16th of a patch but that this was challenging to implement practically. The Subcommittee considered it was unlikely there was any significant unmet health need, as long as the funded oestrogen patches were a matrix patch product.

7.19. The Subcommittee considered oestradiol and oestradiol valerate addressed the same health need however noted the chemicals had slightly different potencies. The Subcommittee noted the current oestradiol valerate tablets could not be divided, due to the tablet coating, and considered this made low dosing difficult. The Subcommittee noted oestradiol tablets could be divided.

7.20. The Subcommittee considered there was a limited role for oestradiol and oestradiol valerate tablets in people requiring low doses. The Subcommittee considered people requiring oral pubertal induction would require low doses, as well as people who react to the currently funded patches. The Subcommittee considered the group of people requiring low-dose, oral oestradiol treatment was likely to be small, but that there would be an important unmet health need if low dose oral oestradiol treatment was unavailable.

7.21. The Subcommittee considered patients would usually be started on low doses in combination packs. The Subcommittee considered there was a group of patients who prefer oral therapy (eg a tablet once a day) to other treatments (eg patches twice a week). The Subcommittee noted there is no funded combined patch, so if combination therapy was required, prescribers currently prescribe oral therapy. The Subcommittee considered prescribers would likely start with two co-prescribed products to allow titration of each one independently rather than a combination product.

7.22. The Subcommittee considered conjugated oestrogens with bazedoxifene has never been well adopted by prescribers in New Zealand however considered there to be a niche role in treatment of patients with an intolerance to progestogens.

7.23. The Subcommittee considered there was an equity issue in this group due to the part-charges on many of the products. Members were supportive of work to remove the part-charges in the future, and considered this could be further discussed at future meetings.

Other Oestrogen Preparations

7.24. The Subcommittee noted the information provided regarding pharmaceuticals in the Other Oestrogen Preparations therapeutic subgroup.

7.25. The Subcommittee considered there was a shift to 'body-identical' oestrogens for use in symptomatic management. The Subcommittee considered patients requiring pubertal induction would likely be started with a patch/ethinyloestradiol and then transitioned on to combined products. The Subcommittee considered seeking advice from the Reproductive and Sexual Health Subcommittee in regard to usage and expenditure in this therapeutic subgroup.

Other Progestogen Preparations

7.26. The Subcommittee noted the information provided regarding pharmaceuticals in the Other Progestogen Preparations therapeutic subgroup.

Thyroid and Antithyroid Agents

7.27. The Subcommittee noted the information provided regarding pharmaceuticals in the Thyroid and Antithyroid Agents therapeutic subgroup.

7.28. The Subcommittee noted there had been previous dosing errors with oral liquid thyroxine, leading to significant negative clinical outcomes. The Subcommittee considered that these dosing errors may, in part, be due to two compounded strengths of oral liquid thyroxine. The Subcommittee considered this risk could be significantly reduced with a proprietary product, but noted there was no New Zealand proprietary product with Medsafe-approval currently available.

7.29. The Subcommittee also noted the current compounded oral liquid thyroxine products are unstable and therefore require a new dispensing every week. The Subcommittee highlighted paediatric patients are moved on to tablets as soon as they can ingest solids (with the tablets crushed up into solid food).

7.30. The Subcommittee considered the short-interval risk of small babies being exposed to double dosing and considered the primary issue to be in babies less than six months of age. The Subcommittee considered it likely a proprietary liquid would be used for longer if funded (ie beyond paediatric patients moving on to solids). The Subcommittee considered a proprietary product would be used in both community and hospital settings.

7.31. The Subcommittee considered there is a small group of women going into pregnancy for whom propylthiouracil (PTU) would be more appropriate than carbimazole. The Subcommittee considered it likely there would be no increase in patient numbers if PTU was open listed.

7.32. The Subcommittee considered there was no unmet health need which would be addressed by whole thyroid extract and that whole thyroid extract should not be funded. The Subcommittee considered the evidence for T3 to be mixed and that there was no appetite for a funded T3 product in the prescribing community. However, the Subcommittee considered there is often patient interest in this product. The Subcommittee noted the recent American Thyroid Association guidelines, which noted there was no indication for the use of T3 alone for the treatment of hypothyroidism.

Trophic Hormones

7.33. The Subcommittee noted the information provided regarding pharmaceuticals in the Trophic Hormones therapeutic subgroup.

7.34. The Subcommittee noted the lowest strength of the currently funded somatropin brand (Omnitrope 5 mg) was contraindicated in patients under 12 months of age as it contained benzyl alcohol. The Subcommittee considered, in practice, the 10 mg presentation was being used although highlighted a wastage issue associated with using this product. The Subcommittee considered the patients under the age of 12 months who required growth hormone therapy would mostly be managed in the community.

Vasopressin Agonists

7.35. The Subcommittee noted the information provided regarding pharmaceuticals in the Vasopressin Agonists therapeutic subgroup.

7.36. The Subcommittee noted the recent listing of desmopressin wafers, following notification of an upcoming long term out of stock of desmopressin nasal drops. The Subcommittee noted advice from members had considered that desmopressin wafers would address the unmet health need during this out of stock. The Subcommittee considered the practical difficulties of dosing titration with desmopressin nasal drops while the wafers could be dissolved and easily titrated. The Subcommittee highlighted the wafers needed to be dissolved to be administered although indicated they could also be placed under the patient's cheek which would then need to be rubbed firmly.

7.37. The Subcommittee considered the majority of patients requiring desmopressin wafers would then transition to desmopressin tablets in childhood. The Subcommittee considered the equity issue resulting from having to crush up tablets and mix into food, given this was not suitable for young paediatric patients.

Other Endocrine Agents

7.38. The Subcommittee noted the information provided regarding pharmaceuticals in the Other Endocrine Agents therapeutic subgroup.

7.39. The Subcommittee considered there was still a clinical need for clomifene citrate in ovulation induction which would not be addressed by other funded alternatives.

Drugs Affecting Bone Metabolism

7.40. The Subcommittee noted the information provided regarding pharmaceuticals in the Drugs Affecting Bone Metabolism therapeutic subgroup.

7.41. The Subcommittee considered pamidronate was still the preferred option for neonatal patients as there is minimal to no published evidence for the safety of other treatment options in this patient group. The Subcommittee considered these patients have the highest rate of respiratory decompensation. The Subcommittee considered the lowest funded strength of pamidronate was used in neonatal patients, to treat hypercalcaemia resulting from calcium metabolism disorders. The Subcommittee considered pamidronate may also be used by haematologists.

Horizon Scanning

7.42. Members highlighted the following items in regard to treatments for endocrine disease:

7.42.1. Burosumab in children with X-linked hypophosphatemia and people with tumour induced osteomalacia. Members highlighted a randomised phase 3 trial by Imel et al (Lancet. Jun 2019) regarding burosumab versus conventional therapy in children with X-linked hypophosphatemia.

7.42.2. Long-acting growth hormones. Members noted some patients in New Zealand were participating in trials for these and highlighted that some patients experience greater levels of discomfort and lipo-atrophy around the injection site when compared with the currently funded growth hormones. The Subcommittee considered this consistent with patient experience of long-acting injection presentations across therapies.

7.42.3. Pasireotide for Cushing's disease.

7.42.4. Asfotase alfa in perinatal- , infantile- and juvenile-onset hypophosphatasia. Members noted it would be likely PHARMAC would receive NPPA applications for this treatment.

7.42.5. Anabolic treatments for osteoporosis, including romosozumab. Members noted an increasing trend to use anabolics as a first line treatment in severe osteoporosis.

7.43. Members considered that tyrosine kinase inhibitors should be funded for patients with radioiodine resistant metastatic differentiated thyroid cancer, a patient group which includes fewer than 20 new patients annually.

7.44. Members noted a change in the funded brand of effervescent phosphorus tablet product (from Phosphate-Sandoz to Phosphate Phebra). Members indicated the bioavailability of the new product was lower than that of the previous product and that some patients were now receiving twice the previous dose in order to maintain target phosphate levels. Members considered this may cause non-compliance issues and would require education and implementation support if the funded brand returned to the previous product in order to ensure patients aren't receiving inappropriate doses.

NPPA Applications

7.45. The Subcommittee noted the information provided regarding Named Patient Pharmaceutical Applications (NPPA) in the Hormones Therapeutic Group and Drugs Affecting Bone Metabolism sub-therapeutic group.

8. Micronised progesterone for MHT

Application

8.1. The Subcommittee noted an application from Pharmaco for the use of micronised progesterone (Utrogestan) for menopause hormone therapy, MHT (previously referred to as hormone replacement therapy, HRT).

Recommendation

8.2. The Subcommittee **recommended** 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.

8.3. The Subcommittee made this recommendation based on:

8.3.1. A lowered risk of breast cancer, cardiovascular disease, and fluctuations in mood compared to currently funded options

8.3.2. A lowered risk of clotting and stroke compared to currently funded options for those needing longer term therapies

8.3.3. A more favourable side-effect profile for those who cannot tolerate currently funded options

8.3.4. A currently unmet health need for Māori and Pacific women who are more at risk of early menopause and are at a higher risk of adverse events from currently funded options due to a higher incidence of comorbidities.

Discussion

8.4. The Subcommittee noted that menopause hormone therapy (MHT) is used by a small group of women with moderate to severe symptoms at menopause, the duration of which can last for 8-10 years after the last menstrual period. The Subcommittee noted that currently the MHT consists of oestrogen combined with progestogen for all women with an intact uterus, and that the progestin options in New Zealand have included medroxyprogesterone acetate, norethisterone and dydrogesterone (which was removed in 2010).

8.5. The Subcommittee noted that menopause can significantly impact on a woman's quality of life, is associated with lower levels of health status and work productivity and greater use of health resources (NAMS Practice Guideline. Menopause. 2017;24:728-53). The Subcommittee also noted that concern was raised about MHT safety in 2002 when a premature release of safety information from the Women's Health Initiative Study occurred (Lemay., J Obstet Gynaecol Can. 2002 Sep;24(9):711-5). The Subcommittee considered that this data was shown subsequently to be incorrect and subsequent more complete analysis showed significant benefits in the younger group of women taking MHT within 10 years of their last menstrual period. The Subcommittee considered this resulted in long-term

stigma regarding MHT and that acceptance (and resulting uptake) of MHT among menopausal women is still affected, but has remained relatively stable in recent years.

8.6. The Subcommittee noted that clinical trials have shown that currently funded MHT options pose an increased risk of breast and cardiovascular health complications. The Subcommittee noted that micronised progesterone for MHT has less undesirable effects on cardiovascular, cognitive and breast health than the currently funded options, with no increase in thromboembolic risk, and no increase or attenuated risk of breast cancer (Fournier et al. Breast Cancer Res Treat. 2008;107:103-11, Dartois et al., Int J Cancer 2016 138, 2415–2427).

8.7. The Subcommittee considered that all new clinical trials are using micronised progesterone as the 'status quo' comparator and that it is unlikely that head-to-head data comparing micronised progesterone will become available. The Subcommittee considered new trials using the currently funded agents as the comparators were unlikely, due to trial regulators considering it unethical to conduct a trial where the comparators required are known to increase breast cancer and cardiovascular risk. The Subcommittee also noted that the use of micronised progesterone for MHT is endorsed by international guideline groups, notably the International Menopause Society 2016 guidelines which state that modern progestogens, natural progesterone and selective estrogen receptor modulators optimise metabolic and breast effects. The Subcommittee considered almost all new MHT products currently being trialled contain micronised progesterone, given its therapeutic benefits and its place in international guidelines.

8.8. The Subcommittee considered the unmet health need which would be met by an MHT product that is safe for women to take long-term, as 10-20% of women will have long-term symptoms, and young women with premature ovarian insufficiency will require MHT until the normal age of menopause. The Subcommittee noted that long-term use of MHT using traditional progestin therapy is likely to increase the risk of breast cancer, and in women with additional risk factors and over the age of 60 the risk of deep vein thrombosis increases. The Subcommittee also noted that Māori and Pacific women are over-represented in the group of women at risk of stroke and deep vein thrombosis because of higher incidence of comorbidities such as diabetes, obesity, and hypertension.

8.9. Members were made aware that initial data from the Christchurch Health and Development Study suggests that Māori women are more likely to reach menopause before the age of 40 (ie. early menopause) at six times the rate of non-Māori women. The Subcommittee considered that due to the current cost associated with micronised progesterone (ie. patients self-funding), there is inequitable access to the treatment option currently considered best practice in MHT.

8.10. The Subcommittee noted the E3N cohort study reported that oestrogen in combination with micronised progesterone was the only option in the study that did not increase the relative risk of breast cancer (Fournier et al. Breast Cancer Res Treat. 2008;107:103-11). The Subcommittee also noted the result from a more recent analysis for the same cohort, which reported a slight increase in breast cancer risk in the long-term, which however still remains lower than the risk with synthetic progesterone options (Dartois et al. Int J Cancer. 2016;138:2415-27). The Subcommittee also noted that this study aggregated progesterone and dydrogesterone effects together, which may have an effect on the risk increase over time.

8.11. The Subcommittee noted that micronised progesterone for this indication has been previously considered by PTAC and the Endocrinology Subcommittee, and that at the most recent PTAC meeting where this was considered (in 2016) PTAC requested to see new evidence cited by the Subcommittee, the Dartois et al. (Int J Cancer 2016;138:2415-27) study. The Subcommittee noted that PTAC had not yet reviewed this new evidence.

8.12. The Subcommittee noted a meta-analysis from 2017 investigating oestradiol therapy and breast cancer risk in perimenopausal and postmenopausal women, which concluded that the breast cancer risk varies with the type of progestogen included in the treatment regimen (Yang et al. Gynecol Endocrinol. 2017;33:87-92).

8.13. The Subcommittee noted a meta-analysis of progestogens and venous thromboembolism in menopausal women that concluded there is evidence to show there is no increase in venous thromboembolism risk with the addition of micronised progesterone to transdermal oestrogen compared with norpregnane derivatives (Scarabin PY. Climacteric. 2018;21:341-45).

8.14. Members were made aware of the following evidence when considering micronised progesterone for MHT:

8.14.1. Canonico et al., Maturitas. 2011 Dec;70(4):354-60 Progestogens and venous thromboembolism among postmenopausal women using hormone therapy

8.14.2. Manson et al., JAMA. 2017 Sep 12;318(10):927-938 Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials

8.14.3. Palacios et Mejía., Expert Opin Drug Saf. 2016 Nov;15(11):1515-1525 Progestogen safety and tolerance in hormonal replacement therapy

8.14.4. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel., Menopause. 2017 Jul;24(7):728-753 The 2017 hormone therapy position statement of The North American Menopause Society

8.14.5. Baber et al., Climacteric. 2016 Apr;19(2):109-50 2016 IMS Recommendations on women's midlife health and menopause hormone therapy

8.14.6. Warren., Climacteric. 2018 Aug;21(4):355-357 Vaginal progesterone and the vaginal first-pass effect

8.14.7. Mirkin., Climacteric. 2018 Aug;21(4):346-354 Evidence on the use of progesterone in menopausal hormone therapy

8.14.8. International Menopause Society Webinar. March 23 2021; Progestogens, progestin, progesterone. Why all the confusion? IMS online education module.

8.14.9. Gompel., Climacteric. 2012 Apr;15 Suppl 1:18-25. Micronized progesterone and its impact on the endometrium and breast vs. progestogens

8.14.10. Cordina-Duverger et al., PLoS One. 2013 Nov 1;8(11):e78016 Risk of Breast Cancer by Type of Menopausal Hormone Therapy: A Case-Control Study among Post-Menopausal Women in France

8.15. The Subcommittee noted that micronised progesterone has improved bioavailability compared with currently funded MHT options and can be administered vaginally for those women with side-effects related to systemic use. The Subcommittee also noted that micronised progesterone does not have the adverse interactions with glucocorticoid or androgen receptors that lead to weight gain, bloating, and skin problems which are experienced with the currently funded options. The Subcommittee noted that the median duration of use of micronised progesterone or MHT would be approximately 5 years for most women, and that the majority of patients would likely cease treatment once their severe menopause symptoms subside.

8.16. The Subcommittee considered that, for managing menopausal symptoms, approximately 10% of women at menopause would use MHT and that the numbers of patients prescribed MHT likely includes patients treated for other indications (noting the majority of funded MHT products are not subject to funding restrictions). The Subcommittee considered that this would equate to approximately 25,000 women in New Zealand annually. The Subcommittee considered that if micronised progesterone were to be open listed there would be uptake from a younger age group who are at a higher clotting and stroke risk and for whom currently funded options are not appropriate, such as those who have gone through premature menopause or have hypogonadism. The Subcommittee considered the potential increased usage from indications other than those previously noted would be minimal.

8.17. The Subcommittee considered that the cost associated with open listing micronised progesterone would be minimal, especially when taking into consideration the decrease in breast cancer risk, and that any future economic analysis should include the increased risk in breast cancer for comparator agents.

9. Cinacalcet for primary hyperparathyroidism

Background

9.1. The Subcommittee noted that clinical advice regarding cinacalcet for the treatment of hyperparathyroidism has been sought from PTAC and PTAC Subcommittees on many occasions from 2008 to 2016 (refer to the PHARMAC Application Tracker for full information).

9.2. The Subcommittee noted that there was a history of Exceptional Circumstances (EC) applications, and subsequently, Named Patient Pharmaceutical Assessments (NPPA) applications for cinacalcet for hyperparathyroidism, including primary hyperparathyroidism. The Subcommittee noted that, by 2015, PHARMAC staff had developed decision maker-approved criteria to guide their assessment of cinacalcet NPPA applications and that the volume of cinacalcet NPPA applications led PHARMAC to previously seek clinical advice to inform its consideration of a Pharmaceutical Schedule listing for cinacalcet.

9.3. The Subcommittee noted that the most recent advice from PTAC in May 2016 recommended that funding of cinacalcet in the Pharmaceutical Schedule for patients with non-malignant primary hyperparathyroidism with symptomatic hypercalcaemia contraindicated to surgery, or where previous surgery has been unsuccessful, be declined. At that time, PTAC considered that insufficient new evidence had been provided to support a positive funding recommendation, and PTAC had considered that it was not appropriate to extrapolate the evidence in patients with parathyroid carcinoma, as this was a different disease.

9.4. The Subcommittee noted that clinically there is a strong desire for cinacalcet to be funded for the treatment of primary hyperparathyroidism in this patient group despite the lack of direct evidence of its effect on mortality and morbidity. The Subcommittee noted that PHARMAC had requested additional advice to help it assess and determine the next best steps for cinacalcet for the treatment of primary hyperparathyroidism.

Discussion

9.5. The Subcommittee considered that the target patient population is a subset of the population with primary hyperparathyroidism with hypercalcaemia; the target group is either unsuitable for surgery, have declined surgery or have not benefitted from surgery and have significant hypercalcaemia, defined as albumin-adjusted calcium >3.0 mmol/L with or without symptoms of hypercalcaemia, or >2.85 mmol/L with symptoms of hypercalcaemia (consistent with the definition used in the NICE guidelines for primary hyperparathyroidism in the UK and Wales; NICE, 2019). The Subcommittee noted the potential for minor variability in laboratory test values across the country but considered >3.0 mmol/L and >2.85 mmol/L to be reasonable thresholds for defining this population.

9.6. The Subcommittee considered that these patients may present with a wide range of clinical manifestations non-specific to primary hyperparathyroidism itself (eg persistent hypercalcaemia, fracture, renal stones, hypercalciuria, osteoporosis), and may include a neurocognitive presentation with psychotic episodes occurring every few months. The Subcommittee noted that people with primary hypercalcaemia are also at risk of excess death from heart or lung causes. The Subcommittee considered that people with acute symptomatic hypercalcaemia may also require acute interventions for management.

9.7. The Subcommittee estimated that the target group may consist of 6-10 new patients per year nationwide, based on case numbers in Auckland and Christchurch. The Subcommittee considered that most of these patients would likely require treatment when aged in their 70s and 80s and therefore some annual mortality would also be expected, and a very small number of patients may require treatment for many years. The Subcommittee considered that an exceptional number of patients (less than one per year) with rare genetic syndromes might require treatment from a younger age. The Subcommittee considered a patient deemed as not being operable (ie not a candidate for surgery) would likely be considered non-operable for life.

9.8. Members noted the surgical procedure is complex and, in some patients, may not be deemed feasible or suitable in the surgical or multi-disciplinary team's opinion (eg due to co-morbidities), or surgery may not be successful in achieving the intended clinical outcomes. In addition, the Subcommittee noted that not all patients may judge their proposed surgery to be beneficial when compared with its risks, and thus that informed consent may not be provided by these patients for anaesthesia and the surgical procedure itself.

9.9. The Subcommittee considered that there is a lack of evidence to inform whether primary hyperparathyroidism disproportionately affects Māori and Pacific peoples, although noted that these populations may experience greater comorbidity than non-Māori and non-Pacific people.

9.10. The Subcommittee noted that cinacalcet is taken orally and can be titrated to achieve a reduction in calcium levels to below 3.0 mmol/L and/or treatment of

symptoms. The Subcommittee considered that there is evidence that elevated calcium levels are associated with symptoms, and that a reduction in calcium level is associated with symptom improvement. The Subcommittee considered the goal of treatment in this patient group is to reduce serum calcium levels to <3.0 mmol/L (rather than reducing parathyroid hormone levels), as <3.0 mmol/L is considered a 'safe' serum calcium level that reduces the risks of neurocognitive complications of hypercalcaemia, and of episodes of acute severe hypercalcemia.

9.11. The Subcommittee considered that new evidence to inform the assessment of cinacalcet in this primary hyperparathyroidism was limited, however, members were made aware of evidence from the following publications (of which, two include cinacalcet for parathyroidectomy non-candidates which referred to hypercalcaemia with unspecified severe symptoms):

9.11.1. The Subcommittee noted an observational cohort study (audit) in Scotland of 2,598 surgical patients admitted with primary hyperparathyroidism (causes of secondary hyperparathyroidism being excluded) between 1986 to 2010 with data followed up until 2011 and including post-surgery outcomes for those who received parathyroidectomy (Collier et al. Endocr Pract. 2019;25:335-9). The Subcommittee noted that 78% of patients included were female, which the Subcommittee considered was a reasonable estimate of female prevalence in this disease.

9.11.1.1. The Subcommittee noted that after follow-up, 41% of the total cohort were deceased and the standardised mortality ratio compared with the general population was 1.58, but that 42% of patients did not have surgery (either they did not meet criteria, or for other reasons), and therefore considered this group was more conservatively treated group than those in New Zealand.

9.11.1.2. The Subcommittee noted that the raw standardised mortality ratio compared to the general population was 1.30 in patients who received surgery (58% of the cohort) and was 1.88 in patients who were treated conservatively; after adjustment for comorbidity, the latter reduced to 1.49 (95% CI: 1.30 to 1.70; P<.0001). The Subcommittee considered the conservatively treated group was similar to the target New Zealand population for this indication. Based on this, the Subcommittee considered that hyperparathyroidism increases mortality compared with the general population; that surgery can reduce this mortality; and therefore, that it was reasonable to infer that cinacalcet may provide the same or similar benefit as surgery by reducing mortality by reducing serum calcium levels.

9.11.2. The Subcommittee was made aware of a systematic review and meta regression of cinacalcet in primary hyperparathyroidism (Ng et al. Endocr Connect. 2020;9:724-35) which included eight trials, none of which the Subcommittee considered provided new information as all had been considered by PTAC or PTAC Subcommittees previously. The Subcommittee noted that 90% of patients had normalisation of calcium levels and 10% had normalisation of parathyroid hormone, however, no other endpoints (eg quality of life) or outcomes for mortality and morbidity were discussed in the publication.

9.11.3. The Subcommittee was made aware of an 8-year retrospective observational cohort study in Scotland of 611 patients with primary hyperparathyroidism seen in secondary care between 2006 and 2014, of which 337 patients did not

receive surgery (Reid et al. J Clin Endocrinol Metab. 2019;104:3692-700). The Subcommittee noted that after an 8-year period of follow-up, the mortality rate was 16.0% (98/611) overall, with about 30% of deaths due to cancer and about 30% due to cardiovascular disease. The Subcommittee noted that 79 deaths were reported in the group who did not receive surgery. The Subcommittee noted associations between mortality and increasing age, social deprivation, and elevated adjusted calcium levels at diagnosis that were statistically significant, but no associations with parathyroid hormone levels at diagnosis. The Subcommittee considered that the study population was similar to the target New Zealand population for this indication and was the most representative evidence for the target New Zealand population. The Subcommittee considered it may not be feasible to do an appropriately powered intervention study in this population.

9.11.4. The Subcommittee noted an observational cohort study derived from a random population sample of 750 50-year-old men in Sweden that described a 21 year follow up of men with primary hyperparathyroidism, and which did not show evidence for long term complications nor a mortality difference. The Subcommittee noted this study reported very wide confidence intervals (Kontogeorgos et al. Scand J Clin Lab Invest. 2020;80:6-13).

9.12. The Subcommittee noted that UpToDate suggests cinacalcet be used for patients with symptomatic primary hyperparathyroidism who are unable to have surgery (whose primary indication for surgery is symptomatic and/or severe hypercalcemia), and that cinacalcet would be more appropriate than bisphosphonates where bone density is normal, as supported by literature review updated in April 2021.

9.13. The Subcommittee noted that the previously mentioned NICE guidelines for primary hyperparathyroidism in the UK and Wales (NICE, 2019) recommend cinacalcet be used for patients in whom surgery fails or is denied, to treat symptomatic patients with calcium over 2.85 mmol/L and patients with calcium levels of >3.0 mmol/L with or without symptoms. Members noted that the NICE guidelines state that bisphosphonates should not be used for chronic hypercalcaemia of primary hyperparathyroidism.

9.14. The Subcommittee considered that there is evidence of improved mortality from secondary hyperparathyroidism in patients on renal dialysis in particular, and that this comorbid population experiences high event rates and pathology-related mortality from hypercalcaemia and secondary hyperparathyroidism, due to the toxicity of the parathyroid hormone.

9.15. Overall, the Subcommittee considered that existing evidence for efficacy of cinacalcet in reducing serum calcium in primary hyperparathyroidism is robust. The Subcommittee considered the health benefit for hypercalcaemia is based on biochemical and end-organ endpoints after surgery (which the Subcommittee considered provides strong evidence), and that there is a lack of evidence for reduced mortality in the population with primary hypercalcaemia following treatment with cinacalcet.

9.16. The Subcommittee considered that there was no new evidence of biochemical efficacy of cinacalcet in reducing serum calcium, although existing evidence for this is robust and that there was strong evidence for cinacalcet compared with surgery in normalising calcium levels (but not in reducing parathyroid hormone levels).

Summary

9.17. The Subcommittee considered 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 with primary hyperparathyroidism, whereas that a reduction in parathyroid hormone was not the target outcome for this group.

9.18. The Subcommittee considered 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. The Subcommittee considered that, while there was limited evidence for the effect of cinacalcet on endpoints such as cardiovascular outcomes, fractures and mortality, it was reasonable to assume that a clinically significant reduction in calcium levels would be associated with improvement in these endpoints.

9.19. The Subcommittee considered it 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. Members noted many such patients would experience neurocognitive effects from elevated calcium. The Subcommittee considered that if funded for this population, cinacalcet would be a chronic intervention to keep calcium low and that, if tolerated and effective in reducing calcium levels, treatment with cinacalcet could be lifelong, or otherwise treatment would be discontinued.

9.20. The Subcommittee noted that there was a lack of evidence to inform the frequency and management of interventions to manage acute symptomatic hypercalcaemia, which would incur clinical costs for close observation, monitoring and short-term management. The Subcommittee considered that data regarding quality of life, long-term complications and hospitalisations is not available within the published clinical trial evidence and would need to be obtained from authoritative guidelines and clinician advice.

9.21. The Subcommittee considered that, if criteria were to be applied to target funding of cinacalcet to this population with primary hyperparathyroidism, all the following would need to be incorporated: hypercalcaemia of >3 mmol/L with or without symptoms, or >2.85 mmol/L with symptoms; the patient is not deemed operable, or surgery has failed or is contraindicated; and the patient has other comorbidities, severe bone pain, or calciphylaxis.

10. Denosumab for osteoporosis

Application

10.1. The Subcommittee noted that PHARMAC had received correspondence, including from Subcommittee members, seeking amendment to the Special Authority criteria for denosumab.

10.2. The Subcommittee noted that this item did not relate to a particular application or seek review of specific evidence. The Subcommittee was asked to consider potential amendments to the Special Authority criteria for denosumab.

Recommendation

10.3. The Subcommittee **recommended** that the Special Authority criteria for denosumab for people for whom bisphosphonates are contraindicated be amended with a **high**

priority, within the context of treatment of endocrine disease, with the proposed criteria (to replace the current criteria) as follows:

DENOSUMAB
Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. The patient has established osteoporosis; and
2. Any of the following:
    - 2.1. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically and documented bone mineral density (BMD) T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA); or
    - 2.2. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically, and either the patient is 75 years of age or older, or densitometry scanning cannot be performed because of logistical, technical or pathophysiological reasons; or
    - 2.3. History of two significant osteoporotic fractures, as defined by the WHO, demonstrated radiologically; or
    - 2.4. Documented T-score less than or equal to -3.0, measured using DEXA; or
    - 2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements, measured using DEXA; and
3. Either:
    - 3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or
    - 3.2. The patient has experienced at least one symptomatic new fracture or a BMD loss greater than 2% per year, after at least 12 months' continuous therapy with a funded antiresorptive agent.

10.4. In making this recommendation, the Subcommittee considered the health need, lack of suitable alternative treatments, health benefits, suitability, and access equity.

10.5. The Subcommittee **recommended** that the Special Authority criteria for denosumab for people in whom bisphosphonates are <u>contraindicated, ineffective or not tolerated</u> be amended with a **high priority**, within the context of treatment of endocrine disease, with the proposed criteria (to replace the current criteria) as follows:

DENOSUMAB
Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. The patient has established osteoporosis; and
2. Any of the following:
    - 2.1. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically and documented bone mineral density (BMD) T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA); or
    - 2.2. History of one significant osteoporotic fracture, as defined by the WHO, demonstrated radiologically, and either the patient is 75 years of age or older, or densitometry scanning cannot be performed because of logistical, technical or pathophysiological reasons; or
    - 2.3. History of two significant osteoporotic fractures, as defined by the WHO, demonstrated radiologically; or
    - 2.4. Documented T-score less than or equal to -3.0, measured using DEXA; or
    - 2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements, measured using DEXA; and
3. Any of the following:
    - 3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or
    - 3.2. Bisphosphonates are not tolerated due to GI disturbance, severe acute phase reaction or inflammatory ocular disease; or
    - 3.3. The patient has experienced at least two symptomatic new fractures or BMD loss greater than 2% per year; or
    - 3.4. Intravenous bisphosphonates cannot be administered due to logistical or

technical reasons.

10.6. In making this recommendation, the Subcommittee considered the health need, lack of suitable alternative treatments, benefits, suitability, and access equity.

Discussion

10.7. The Subcommittee noted that denosumab is a monoclonal antibody directed against a key signalling protein for osteoclast development. The Subcommittee noted that denosumab has been used internationally in osteoporosis for more than a decade including use as a first-line agent in many countries, including Australia.

10.8. The Subcommittee noted that denosumab was funded in New Zealand for the treatment of osteoporosis subject to Special Authority criteria in 2018. The Subcommittee noted that some patients with osteoporosis who would benefit from denosumab are unable to access it through the current Special Authority criteria and considered there was a lack of clarity among clinicians with regards to the current criteria. The Subcommittee considered that the Special Authority criteria result in a significant unmet health need for some patients who would receive health benefit from access to funded denosumab and do not have funded alternatives available to them.

10.9. The Subcommittee considered the current Special Authority criteria require prior treatment with bisphosphonates in patients where the use of bisphosphonates may be unsafe (ie in patients with renal impairment) and is inconsistent with clinical guidelines. However, the Subcommittee considered it possible that in some cases, some use of bisphosphonates may occur in practice with modified dosing schedules (eg once a month instead of once weekly treatment) for patients with few suitable options, such as those with significant renal impairment or those where benefits would outweigh risks, such as those with a high risk of fracture. Members considered that this would likely occur as a result of no effective funded alternatives.

10.10. The Subcommittee noted that other funded treatments for osteoporosis include oral or intravenous bisphosphonates, such as intravenous zoledronic acid.

Intolerance or contraindication to bisphosphonates

10.11. The Subcommittee considered that while some patients may experience minor adverse effects after infusion of bisphosphonates, there was an unmet need for patients who truly cannot tolerate first-line treatment with bisphosphonates eg patients very unwell and requiring hospitalisation, or those experiencing gastrointestinal issues with oral bisphosphonates (which the Subcommittee considered may occur in up to one in five people). The Subcommittee considered that there was a need for an effective alternative agent for reducing fracture risk, as an alternative to first-line bisphosphonates.

10.12. The Subcommittee considered that patients may be considered to be intolerant to oral bisphosphonates due to malabsorption issues, oesophageal dysphagia or extensive gastrointestinal surgery, and that malabsorption may impair treatment efficacy.

10.13. The Subcommittee considered that patients could be considered to be intolerant to bisphosphonates for other reasons, such as inflammatory eye disease (rare, but occurring in approximately 6 per 1,000 people) or acute phase reaction (occurring in up to 1 in 5 people, with very severe acute phase reactions in 1 in 200 people);

these would preclude patients from safely receiving further treatment with bisphosphonates. Members considered that for the purposes of targeting funded treatment with denosumab, intolerance to bisphosphonates should be carefully defined.

10.14. The Subcommittee considered that people with renal failure (defined as having eGFR <35 ml/min) comprise a significant proportion of patients within the group of patients for whom bisphosphonates are considered to be contraindicated, as bisphosphonates are renally excreted whereas denosumab is not renally excreted. The Subcommittee noted that clinical trials of bisphosphonates excluded people with eGFR of 35 or less, however, trials with denosumab did not exclude people with eGFR of 35 or less. The Subcommittee noted that, based on the evidence for denosumab in this patient subgroup, denosumab is considered to be safe in patients with renal failure. The Subcommittee considered that it was important to retain a criterion in the denosumab Special Authority for renal function and considered that eGFR was a more relevant measure than creatinine clearance.

10.15. The Subcommittee noted in a US study that, among patients with osteoporosis, 23.8% had renal impairment of eGFR <35 ml/min (Klawansky et al. Osteoporos Int 2003;14:570-6). The Subcommittee considered the likely prevalence in New Zealand to be lower than this.

Administration

10.16. The Subcommittee considered that people who were intolerant to, or had a contraindication to, oral bisphosphonates (eg due to gastrointestinal malabsorption) could reasonably seek access to intravenous bisphosphonates, if available and accessible. However, the Subcommittee considered that there are access inequities resulting from lack of access to funded infusion services and inability to afford unfunded infusion services at a cost of up to $200 per patient per infusion.

10.17. The Subcommittee noted that despite the cost of a pharmaceutical (such as zoledronic acid) being funded, administration costs may be incurred by patients as not all treatment centres fund intravenous infusions and access to unfunded infusion services is variable around the country. The Subcommittee considered that the intravenous administration fee paid by patients, required in some areas in order to receive funded intravenous treatment in the community presents a barrier to access for many patients. The Subcommittee considered that amending funding criteria would support equitable access to an effective treatment option for patients who cannot access infusion services to receive intravenous treatment.

10.18. The Subcommittee considered that almost all people who would receive denosumab would self-administer as it is a subcutaneous injection, however, some patients may have this administered by a district nurse or receive injections in a rest home. The Subcommittee considered that self-administered subcutaneous injections would be manageable for the majority of eligible patients (or, where applicable, their caregivers), however the six-monthly administration may be challenging and result in patients taking longer to learn to self-administer as the long interval between injections would reduce familiarity with the technique.

10.19. The Subcommittee considered, on balance, that six-monthly subcutaneous administration of denosumab would be straightforward for most patients and would be more accessible and provide suitability benefits over intravenous treatments.

Evidence

10.20. The Subcommittee noted that the key phase III trials of denosumab in osteoporosis were published more than a decade ago and considered that there would be no further trials, and in particular, no head-to-head trials investigating denosumab compared with other bisphosphonates. The Subcommittee considered that there is no new data available that has not already been reviewed by the Subcommittee or PTAC and noted the denosumab clinical trial data described in the Medsafe data sheet (Prolia Data Sheet, November 2020). The Subcommittee considered that the efficacy of denosumab in preventing vertebral and non-vertebral fractures is similar to that of other funded bisphosphonates and that it was appropriate for use as a second-line agent in most cases.

10.21. The Subcommittee considered that it would be reasonable to assume that the evidence of health benefit in men and postmenopausal women can be extrapolated to pre-menopausal women, as in all situations including baseline risk, denosumab produces the same relative risk reduction in fractures. The Subcommittee considered that very few pre-menopausal female patients would seek access to denosumab for osteoporosis, therefore amending the criteria to omit gender and postmenopausal criteria would be reasonable.

10.22. The Subcommittee considered that it was reasonable to assume denosumab has similar anti-fracture efficacy to bisphosphonates, as the available evidence indicates that the relative risk reduction and anti-fracture efficacy is similar. The Subcommittee considered that the duration of effect after treatment with bisphosphonates differs depending on the chemical, although the evidence for this is limited.

10.23. The Subcommittee considered that denosumab is effective in reducing fracture risk in patients who cannot receive first-line treatment with bisphosphonates, and was made aware of evidence that indicates denosumab could be safely used in people with renal impairment (Nitta et al. Intern Med 2017;56:3271-76; Khairallah et al. Clin J Am Soc Nephrol. 2018;13:962-9).

10.24. The Subcommittee considered that denosumab could be suitable for young children with bone fragility or osteogenesis imperfecta in their first few weeks of life, and for older children with cerebral palsy or previous fractures currently receiving zoledronic acid, where there are logistical or technical barriers to intravenous infusion services. The Subcommittee considered the majority of children would not be eligible under the proposed Special Authority criteria (given different definitions, the diagnostic requirements and differences in disease scoring in the paediatric setting, particularly for neonates), and that this should be discussed at a future meeting.

DEXA and fractures

10.25. The Subcommittee noted that the incidence of hip fractures increases with age. The Subcommittee considered that the FRAX algorithm (to estimate all hip fracture probabilities) and the Garvan algorithm (for estimating the probability of all osteoporotic fractures) are essentially the same at a population level.

10.26. The Subcommittee noted access to DEXA scanning would vary around the country. The Subcommittee considered that patients younger than 75 years of age who cannot access DEXA may meet the denosumab funding criteria based on the threshold for fracture risk instead.

10.27. The Subcommittee considered that it was reasonable to retain the Special Authority criterion regarding fractures occurring while on bisphosphonates, as bone loss

occurring while on bisphosphonates would indicate that further treatment should be considered. The Subcommittee did not consider it appropriate to switch treatment based on one fracture.

10.28. The Subcommittee considered that the Special Authority criteria should be amended for clarity, to present the criteria for the targeted population more simply. The Subcommittee considered that severe osteoporosis was not a clinically recognised term and should be removed from the criteria. The Subcommittee considered that the definition of an osteoporotic fracture would be variable in practice, although fractures in the smaller bones of the hands, feet and skull would not be considered fragility fractures.

Costs and savings

10.29. The Subcommittee considered that the costs of not effectively treating patients at risk of fractures was significant due to the high cost of hospital admission and extended stay in hospital to manage a hip fracture for example, in addition to transfer to a rest home which may be required for many older patients. Members considered that these costs were significant and far-reaching, with impacts on the health system. Despite the drug cost of denosumab being considerably higher than that of bisphosphonates, the Subcommittee considered that there would be a reduction in other costs due to prevention of fractures in patients who could not receive bisphosphonates as first-line treatment for osteoporosis.

Special Authority amendments

10.30. The Subcommittee considered the following amendments would need to be made to the current Special Authority criteria for denosumab to widen funded treatment to those for whom bisphosphonates are contraindicated:

DENOSUMAB
Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:

1. The patient has ~~severe,~~ established osteoporosis; and
~~2. Either:~~
~~2.1. The patient is female and postmenopausal; or~~
~~2.2. The patient is male or non-binary; and~~
2. Any of the following:
2.1. History of one significant osteoporotic fracture**, as defined by the WHO,** demonstrated radiologically and documented bone mineral density (BMD) **T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA)** ~~greater than or equal to 2.5 standard deviations below the mean normal value in young adults (ie T-Score less than or equal to -2.5) (see Note)~~; or
2.2. History of one significant osteoporotic fracture**, as defined by the WHO,** demonstrated radiologically, and either the patient is **75 years of age or older** ~~elderly~~, or densitometry scanning cannot be performed because of ~~major~~ logistical, technical or pathophysiological reasons; or
2.3. History of two significant osteoporotic fractures**, as defined by the WHO,** demonstrated radiologically; or
2.4. Documented T-score less than or equal to -3.0**, measured using DEXA** ~~(see Note)~~; or
2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements**, measured using DEXA** ~~(see Note)~~; **and** ~~or~~
~~2.6. Patient has had a Special Authority approval for alendronate (Underlying cause - Osteoporosis) prior to 1 February 2019 or has had a Special Authority approval for raloxifene; and~~
3. Either:
3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or
3.2. The patient has experienced at least two symptomatic new fractures or BMD loss

greater than 2% per year.

4. ~~Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 ml/min; and~~
5. ~~The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes); and~~
6. ~~The patient must not receive concomitant treatment with any other funded antiresorptive agent for this condition or teriparatide.~~

~~Note~~

~~a) BMD (including BMD used to derive T-Score) must be measured using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable~~

~~b) Evidence suggests that patients aged 75 years and over who have a history of significant osteoporotic fracture demonstrated radiologically are very likely to have a T-Score less than or equal to -2.5 and, therefore, do not require BMD measurement for treatment with denosumab~~

~~c) Osteoporotic fractures are the incident events for severe (established) osteoporosis and can be defined using the WHO definitions of osteoporosis and fragility fracture. The WHO defines severe (established) osteoporosis as a T-score below -2.5 with one or more associated fragility fractures. Fragility fractures are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture (minimal trauma). The WHO has quantified this as forces equivalent to a fall from a standing height or less~~

~~d) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body~~

~~e) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: risedronate sodium tab 35 mg once weekly; alendronate sodium tab 70 mg or tab 70 mg with cholecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialled so that the patient achieves the minimum requirement of 12 months' continuous therapy~~

10.31. The Subcommittee considered the following amendments would need to be made to the current Special Authority criteria for denosumab to widen funded treatment to those for whom bisphosphonates are contraindicated, ineffective or not tolerated:

DENOSUMAB

Initial application – from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:

1. The patient has ~~severe,~~ established osteoporosis; and
2. ~~Either:~~
   - 2.1. ~~The patient is female and postmenopausal; or~~
   - 2.2. ~~The patient is male or non-binary; and~~
2. Any of the following:
   - 2.1. History of one significant osteoporotic fracture**, as defined by the WHO,** demonstrated radiologically and documented bone mineral density (BMD) **T-score less than or equal to -2.5, measured using dual-energy x-ray absorptiometry (DEXA)** ~~greater than or equal to 2.5 standard deviations below the mean normal value in young adults (ie T-Score less than or equal to -2.5) (see Note)~~; or
   - 2.2. History of one significant osteoporotic fracture**, as defined by the WHO,** demonstrated radiologically, and either the patient is **75 years of age or older** ~~elderly~~, or densitometry scanning cannot be performed because of ~~major~~ logistical, technical or pathophysiological reasons; or
   - 2.3. History of two significant osteoporotic fractures**, as defined by the WHO,** demonstrated radiologically; or
   - 2.4. Documented T-score less than or equal to -3.0**, measured using DEXA** ~~(see Note)~~; or
   - 2.5. A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements**, measured using DEXA** ~~(see Note)~~; **and**~~or~~
   - ~~2.6. Patient has had a Special Authority approval for alendronate (Underlying cause – Osteoporosis) prior to 1 February 2019 or has had a Special Authority approval for raloxifene; and~~
3. **Any of the following:**
   - **3.1. Bisphosphonates are contraindicated because the patient's eGFR is less than 35 ml/min; or**

3.2. Bisphosphonates are not tolerated due to GI disturbance, severe acute phase reaction or inflammatory ocular disease; or

3.3. The patient has experienced at least two symptomatic new fractures or BMD loss greater than 2% per year; or

3.4. Intravenous bisphosphonates cannot be administered due to logistical or technical reasons.

~~4. Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 ml/min; and~~

~~5. The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes); and~~

~~6. The patient must not receive concomitant treatment with any other funded antiresorptive agent for this condition or teriparatide.~~

~~Note~~

~~a) BMD (including BMD used to derive T-Score) must be measured using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable~~

~~b) Evidence suggests that patients aged 75 years and over who have a history of significant osteoporotic fracture demonstrated radiologically are very likely to have a T-Score less than or equal to -2.5 and, therefore, do not require BMD measurement for treatment with denosumab~~

~~c) Osteoporotic fractures are the incident events for severe (established) osteoporosis and can be defined using the WHO definitions of osteoporosis and fragility fracture. The WHO defines severe (established) osteoporosis as a T-score below -2.5 with one or more associated fragility fractures. Fragility fractures are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture (minimal trauma). The WHO has quantified this as forces equivalent to a fall from a standing height or less~~

~~d) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body~~

~~e) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: risedronate sodium tab 35 mg once weekly; alendronate sodium tab 70 mg or tab 70 mg with cholecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialled so that the patient achieves the minimum requirement of 12 months' continuous therapy~~

Summary

10.32. Overall, the Subcommittee considered that if bisphosphonates are not able to be used (ie contraindicated, ineffective or not tolerated), there should be a funded alternative for these patients. Therefore, the Subcommittee supported widening access to include these patients in the amended criteria for denosumab. The Subcommittee considered it was uncertain how many patients would experience bone loss on first-line bisphosphonate therapy and may therefore require a second-line therapy.

10.33. The Subcommittee considered that the Special Authority criteria for denosumab could be refined to better align with standard recommendations and detail clinical criteria reflecting an intolerance of bisphosphonates, or inability to access intravenous bisphosphonates. The Subcommittee considered that the proposed Special Authority criteria would accurately target those intended for funding and that removing the criteria describing adequate doses of antiresorptive agents would not be likely to increase the number of patients accessing denosumab.

10.34. The Subcommittee considered that patients with intolerance to bisphosphonates currently have no effective funded alternative treatment and therefore the Subcommittee supported widening access to denosumab to provide such an alternative. The Subcommittee noted that this group would include patients who were unable to access intravenous treatment due to cost, although the size of this patient subgroup was unknown.

10.35. The Subcommittee considered that while appropriate use of denosumab would be as a second-line agent in most cases, there would be clear delineation in clinical practice between first line use of bisphosphonates (if not contraindicated), and then denosumab if bisphosphonates were contraindicated or not tolerated.

11. Osteoporosis treatments

Application

11.1. The Subcommittee noted a paper from PHARMAC staff regarding the currently funded osteoporosis treatments. The Subcommittee noted this paper was being considered in order to rationalise and harmonise the available osteoporosis treatments.

Recommendations

11.2. The Subcommittee **recommended** that funding restrictions for zoledronic acid be removed with a **high priority** within the context of treatment of endocrine disease.

11.3. In making this recommendation, the Subcommittee considered the high health need of patients with osteoporosis, improved suitability of the treatment (reduced infusion interval), cost of treatment compared to available alternatives (ie funded oral antiresorptive agents) and cost-effectiveness to the health sector.

11.4. The Subcommittee **recommended** the following Special Authority for teriparatide (to replace the current criteria) with a **medium priority**, in the context of treatment of endocrine disease:

> **TERIPARATIDE**
> **Initial application** – from any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:
>
> All of the following:
> 1. The patient has a documented T-score less than or equal to -3.0, measured using dual energy x-ray absorptiometry (DEXA); and
> 2. Either:
> 2.1 The patient has had two or more fractures due to minimal trauma; or
> 2.2 The patient has had a clinical vertebral fracture.

11.5. In making this recommendation, the Subcommittee considered the health benefit, availability of existing treatments and cost-effectiveness.

11.6. The Subcommittee **recommended** raloxifene be delisted.

11.7. In making this recommendation, the Subcommittee considered the minimal health benefit from raloxifene, low cost-effectiveness and greater efficacy of available alternative treatments.

Discussion

Zoledronic acid

11.8. The Subcommittee noted that fractures are common in patients with osteoporosis and that, currently, bisphosphonates are the first-choice treatment to reduce fracture risk. The Subcommittee noted alendronate and risedronate are both oral agents, taken as a weekly tablet and that neither is subject to funding restrictions.

11.9. The Subcommittee noted that zoledronic acid 5 mg per 100 ml is an intravenous (IV) agent, at a current cost to the pharmaceutical budget of approximately $60 per 5 mg dose. The Subcommittee noted that zoledronic acid is subject to funding restrictions. The Subcommittee did not consider the funding restrictions resulted in access inequities.

11.10. The Subcommittee considered the fracture risk reduction was comparable between zoledronic acid and oral bisphosphonates, but that persistence was likely to be greater for zoledronic acid. The Subcommittee considered that zoledronic acid is a convenient treatment option for many individuals with osteoporosis, however also considered that there was inconsistent availability in secondary care and that there is an infusion cost to the patient for administration in many primary care practices of up to $200 per patient per infusion.

11.11. The Subcommittee noted oral bisphosphonates are associated with gastrointestinal side effects and that IV agents are associated with acute phase reactions. The Subcommittee noted that neither are recommended for patients with renal failure with creatinine clearance less than 35 ml/min. The Subcommittee considered there would be no appreciable extra health sector costs from the current Special Authority criteria (eg resulting from management of side effects). The Subcommittee considered that the incidence of significant side effects from zoledronic acid (eg acute phase reactions) were decreasing with the move from re-treatment every 12 months to every 18 months.

11.12. The Subcommittee noted that, for the majority of patients with Paget's disease of the bone, one zoledronic acid infusion would supress disease activity for more than five years and therefore the financial risk in this patient group is very low if the Special Authority were to be removed.

11.13. The Subcommittee considered that patients with established osteoporosis (and a resulting high fracture risk) require effective and readily available therapies. The Subcommittee considered that the health benefit of zoledronic acid in the treatment of osteoporosis was significant. The Subcommittee considered treatment with oral and IV bisphosphonates to be relatively inexpensive in the context of endocrine treatments.

11.14. The Subcommittee considered it likely that patient numbers would increase if funding restrictions were removed as some patients would shift from the currently funded oral bisphosphonate agents to zoledronic acid. The Subcommittee considered the number of additional patients who would receive zoledronic acid was uncertain; however, patients being managed in secondary care would be more likely to move to zoledronic acid if restrictions were removed, compared to those patients managed in primary care.

11.15. The Subcommittee considered that zoledronic acid would continue to be used for indications currently funded (both for the 4 mg and 5 mg dose). The Subcommittee considered that if funding restrictions were removed, zoledronic acid would also be used for the treatment of severe hypercalcaemia of any cause.

11.16. The Subcommittee suggested PHARMAC considers funding the 4 mg zoledronic acid presentation for osteoporosis, instead of the currently funded 5 mg dose, given the 4 mg presentation is less expensive. The Subcommittee considered that, while the 4 mg dose is not Medsafe-approved for treatment of osteoporosis and there was no available fracture outcomes data specific to this presentation, there were good

surrogate marker data indicating efficacy of doses lower than 5 mg (Reid et al., N Engl J Med. 2002 Feb 28;346(9):653-61).

Teriparatide

11.17. The Subcommittee considered that the evidence suggests that teriparatide is less efficacious if used as a second-line treatment after bisphosphonates. The Subcommittee considered that teriparatide would provide significant health benefit for a small group of patients with a clinical vertebral fracture, if used as a first line agent in severe osteoporosis. The Subcommittee considered that bisphosphonates would then be used second line for these patients.

11.18. The Subcommittee noted that there was variation in terminology in radiology reporting regarding vertebral fractures, however, considered that clinicians would interpret 'clinical vertebral fracture' as a painful vertebral fracture or painless compression fracture.

11.19. The Subcommittee considered that there would be a small increase in the number of patients seeking access to funded teriparatide if the funding restrictions were amended to include patients with a clinical vertebral fracture and total hip or spine BMD T-score of less than -3.0. The Subcommittee did not consider that this would create any access inequities compared to the current Special Authority criteria.

11.20. The Subcommittee considered the following amendments would need to be made to the current Special Authority criteria for teriparatide to rationalise and harmonise funded treatment for patients with osteoporosis:

TERIPARATIDE
Initial application – from any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:

All of the following:
~~1. The patient has severe, established osteoporosis; and~~
2. The patient has a documented T-score less than or equal to -3.0**, measured using dual energy x-ray absorptiometry**; and
3. Either:
3.1 The patient has had two or more fractures due to minimal trauma**; or**
3.2 **The patient has had a clinical vertebral fracture.**
~~3.2 The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes).~~

~~Note~~
~~a) The bone mineral density (BMD) measurement used to derive the T-score must be made using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable~~
~~b) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: alendronate sodium tab 70 mg or tab 70 mg with colecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily; zoledronic acid 5 mg per year. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialled so that the patient achieves the minimum requirement of 12 months' continuous therapy.~~
~~c) c) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.~~
~~d) d) A maximum of 18 months of treatment (18 cartridges) will be subsidised.~~

Raloxifene

11.21. The Subcommittee noted that raloxifene is not effective in preventing non-vertebral fractures as it is a weak anti-resorptive agent. The Subcommittee considered that raloxifene did not provide a cost-effective treatment option, given that it increases the risk of venous thromboembolic disease and vasomotor flushes. The Subcommittee considered that de-emphasising raloxifene, any amendments to the Special Authority or delisting raloxifene would have little (if any) impact on the health system given its current limited usage.

12. Eplerenone for primary aldosteronism

Application

12.1. The Subcommittee noted an application regarding the widening of access to eplerenone to patients with primary aldosteronism who are intolerant to spironolactone.

Recommendation

12.2. The Subcommittee **recommended** that eplerenone for the treatment of primary aldosteronism for patients intolerant to spironolactone be listed with a **high priority**, within the context of treatment of endocrine disease, subject to the following Special Authority criteria:

> **EPLERENONE**
> **Initial application – (primary aldosteronism)** only from a cardiologist, endocrinologist or nephrologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Both:
> 1 The patient has had a diagnosis of primary aldosteronism; and
> 2 Either:
> 2.1. Patient is intolerant to optimal dosing of spironolactone; or
> 2.2. Patient has experienced a clinically significant adverse effect while on optimal dosing of spironolactone.

12.3. The Subcommittee made this recommendation based on the unmet health need of this patient group, as a result of a lack of a funded alternative, and the health benefit provided by eplerenone, through the prevention of morbidity and mortality as a result of excess aldosterone section and its associated effects. The Subcommittee also noted this recommendation aligned with the government health priorities.

Discussion

12.4. The Subcommittee noted that an application for eplerenone for the treatment of primary aldosteronism was first received in 2015. Eplerenone was funded in 2018 as a potassium-sparing diuretic for patients with heart failure with an ejection fraction less than 40%, who are either intolerant to optimal dosing of spironolactone or have experienced significant adverse effect while on optimal dosing of spironolactone.

12.5. The Subcommittee noted that in 2018, an application was received to widen access to eplerenone for patients with primary aldosteronism and resistant hypertension, in both cases where the patient is intolerant of spironolactone. The Subcommittee noted that this application followed a supplier discontinuation of amiloride tablets, leading to fewer options for treating primary aldosteronism. The Subcommittee noted that this application was considered by the Cardiovascular Subcommittee in May 2019, where the Cardiovascular Subcommittee recommended widening access to eplerenone for patients with primary aldosteronism who are also intolerant

of spironolactone with a high priority. The Subcommittee noted that there has been no new evidence published about eplerenone for the treatment of primary aldosteronism since the Cardiovascular Subcommittee considered this application.

12.6. The Subcommittee also noted that the application was considered by PTAC in August 2019, where the Committee considered that the mechanism of the health benefit for eplerenone in primary aldosteronism and resistant hypertension was likely similar to that of spironolactone, and considered that access to eplerenone for patients with primary aldosteronism who are also intolerant of spironolactone be funded with a high priority and should be further considered by the Endocrinology Subcommittee.

12.7. The Subcommittee noted that primary aldosteronism is the excess production of the hormone aldosterone from the adrenal glands which may be caused by hyperplasia or a tumour. The Subcommittee noted that primary aldosteronism is mainly caused by bilateral idiopathic hyperaldosteronism (also called idiopathic hyperplasia), causing 60 to 70 percent of cases, and unilateral aldosterone-producing adenomas, causing 30 to 40 percent of cases. The Subcommittee also noted that primary aldosteronism can cause fatigue, potassium deficiency (hypokalaemia), high blood pressure (hypertension), poor vision, confusion, headaches, muscular aches and weakness, muscle spasms, low back and flank pain from the kidneys, trembling, tingling sensations, numbness, and excessive urination.

12.8. The Subcommittee noted that the current treatment for primary aldosteronism is spironolactone, which is a non-selective antagonist of the testosterone receptor that reduces systolic and diastolic blood pressure, but can lead to potentially painful gynaecomastia, erectile dysfunction, and decreased libido. The Subcommittee also noted that spironolactone has a relatively slow onset of action, is a once daily oral treatment and is inexpensive. The Subcommittee noted that there are currently no funded alternatives to spironolactone for patients with primary aldosteronism who are intolerant to spironolactone.

12.9. The Subcommittee noted that eplerenone is a selective antagonist against testosterone receptors, and also reduces systolic and diastolic blood pressure with either the same or slightly less efficacy than spironolactone, and that the side effects of eplerenone seem similar to that of placebo arms in clinical trials. The Subcommittee noted that eplerenone has a quicker onset of action than spironolactone, is an oral twice daily tablet and is significantly more expensive than spironolactone. The Subcommittee noted that the dosing of eplerenone for this indication would be a maximum of 200 mg twice daily. The Subcommittee considered that eplerenone could be administered as 400 mg once a day but that twice a day would be the normal dosing regimen and would help minimise potential side effects.

12.10. The Subcommittee noted that the overall treatment goals for patients with primary aldosteronism is to prevent the morbidity and mortality associated with hypertension, hypokalaemia, renal toxicity, and cardiovascular damage, and that excessive secretion of aldosterone is associated with an increased risk of cardiovascular events (which are independent of hypokalaemia), including an increase in left ventricular mass measurements, stroke, myocardial infarction, heart failure, and atrial fibrillation. The Subcommittee noted that the excess cardiovascular risk resolves after appropriate treatment of the mineralocorticoid excess. The Subcommittee noted that treatment goals for primary aldosteronism due to either unilateral or bilateral adrenal disease are the same and include reversal of the adverse cardiovascular effects of hyperaldosteronism, normalisation

of the serum potassium in patients with hypokalaemia, and normalisation of blood pressure.

12.11. The Subcommittee noted that there is not an increased prevalence of primary aldosteronism in the Māori population compared with the European population but noted that Māori do suffer from higher rates of hypertension, although the aetiology of this is unknown. The Subcommittee noted there was also an increased prevalence of hypertension in Pacific populations. The Subcommittee considered that there is strong evidence to support the health benefit of lowering blood pressure with eplerenone in this patient population.

12.12. The Subcommittee considered that that quality-of-life gains if eplerenone were to be funded for the treatment of primary aldosteronism would not differ between patients with primary aldosteronism and those with resistant hypertension and would include a reduction in unpleasant side-effects from spironolactone, and an effective reduction blood-pressure.

12.13. The Subcommittee considered that the number of eligible patients estimated by the Cardiovascular Subcommittee (under 100 new patients each year) to be an underestimate but noted that there is considerable uncertainty in patient numbers. The Subcommittee considered that prevalent patient numbers are more likely to fall in the upper end of the numbers forecast by the applicant (ie in the 1000s). However, the Subcommittee considered the highest approximation of 5000 to be an overestimation. The Subcommittee noted the applicant's forecast of patient numbers was based on a prevalence of hypertension of 31% of adults, a prevalence of primary aldosteronism of 2% of patients with hypertension of which about 50% would be medically treated, and reports of spironolactone intolerance ranging from 8% to 54%.

12.14. The Subcommittee noted that there is a prevalent pool of patients who would be eligible for eplerenone but considered that there is significant uncertainty as to how many patients this would be. The Subcommittee noted that this would include a cohort of men with primary aldosteronism who are currently taking spironolactone and living with the adverse events, as well as most patients who have stopped taking spironolactone due to intolerance and adverse events. The Subcommittee noted that the eligible population would be significantly larger if patients with resistant hypertension were also considered.

12.15. The Subcommittee considered that if eplerenone were to be funded there would be no significant changes to long-term expenditure for the health system, other than direct treatment costs. The Subcommittee considered eplerenone may reduce the frequency with which patients see a specialist, estimating this would change from every 6 weeks to every 3 months. The Subcommittee noted that eplerenone is likely non-inferior to spironolactone in preventing secondary endpoints of primary aldosteronism such as high blood pressure but considered that the eplerenone would provide long-term benefits in prevention of spironolactone related adverse-events and by making available a treatment option to patients intolerant to spironolactone.

13. Other Business

13.1. There was no other business raised.