PHARMAC
TE PĀTAKA WHAIORANGA

Pharmacology and Therapeutics Advisory Committee
Objective advice to Pharmac

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand

**Phone 64 -4-916-7512 - Fax 64-4-460-4995 - www.pharmac.govt.nz**

# Record of the Pharmacology and Therapeutics Advisory Committee Meeting

## Held on 16 August 2024

**This meeting was held online**

## 1. Present:

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

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

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

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

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

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

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

## 3. Summary of recommendations

| | Pharmaceutical and Indication | Recommendation |
|---|---|---|
| 10.1.4 | Voretigene neparvovec (VN) for the treatment of inherited retinal dystrophies caused by pathological biallelic *RPE65* mutations (*RPE65*-IRD), subject to Special Authority criteria | High Priority |
| 12.4 | Ferric carboxymaltose for people with HHT with serum ferritin ≤50 mcg/L or transferrin saturation ≤20% | Decline |

| | | |
|---|---|---|
| 13.4 | Teriparatide for the first line treatment of very high-risk osteoporosis, subject to Special Authority criteria | Low Priority |

## 4. Record of PTAC meeting held 16 & 17 May 2024

4.1. The Committee reviewed the record of the PTAC meeting held on 16 & 17 May 2024

4.2. The Committee accepted the record.

## 5. Action Points

5.1. There are no current actions points.

## 6. Pharmac Update

6.1. The Committee noted the Pharmac Update.

## 7. Devices Update

7.1. Pharmac staff shared an update on progress with its Hospital Medical Devices Programme including achieving a comprehensive list of medical devices hospitals are currently using, service design of new processes for making changes to the List and associated contracts, establishment of a national health technology assessment pathway for devices, and recent engagement about the devices work.

7.2. Members noted the importance of communicating clearly about the scope of products covered on the Pharmac List and Pharmac's role in assessing new and existing technology. Members highlighted the need for a range of perspectives with our expert advice, consideration of sustainability in device assessment, and the potential value for Pharmac devices work to have a broader scope than hospitals.

## 8. Specialist Advisory Committee Records

### Immunisation Advisory Committee

8.1. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee meeting held on 26 March 2024.

8.2. PTAC noted the record including the Advisory Committee's recommendations.

### Cancer Treatments Advisory Committee

8.3. The Committee (PTAC) reviewed the record of the Cancer Treatments Advisory Committee meeting held on 12 April 2024.

8.4. PTAC noted the record including the Advisory Committee's recommendations.

### Diabetes Advisory Committee

8.5. The Committee (PTAC) reviewed the record of the ad-hoc Diabetes Advisory Committee meeting held online on 21 June 2024.

8.6. Members noted this ad-hoc meeting related to clinical aspects of the proposal to fund Insulin Pumps and consumables and Continuous Glucose Monitors (CGMs) and associated Automatic Insulin Delivery (AID) system capability that arose from the feedback received during the public consultation, as well as some new information gathered since the close of consultation.

8.7. PTAC noted the record including the Advisory Committee's recommendations.

## 9. Correspondence & Matters Arising

### 9.1. Voretigene neparvovec (VN) for the treatment of inherited retinal dystrophies caused by pathological biallelic *RPE65* mutations (*RPE65*-IRD)

**Application**

9.1.1. The Committee reviewed the application for voretigene neparvovec (VN) for the treatment of inherited retinal dystrophies caused by pathological biallelic *RPE65* mutations (*RPE65*-IRD).

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

**Recommendation**

9.1.3. The Committee **recommended** that voretigene neparvovec be listed with a **high priority**, subject to the following Special Authority criteria:

Initial application
Applications from any relevant practitioner
1. Patient has inherited retinal dystrophy; and
2. Patient has documented biallelic RPE65 mutations as determined by a validated test; and
3. Patient has sufficient viable retinal cells as determined by a relevant specialist; and
4. Treatment is to be limited to one treatment per eye per patient lifetime.

9.1.4. The Committee considered the following when making this recommendation:

- the high and unmet health need of people with *RPE65*-IRD
- the reasonable likelihood of a therapeutic benefit beyond 7 years and this benefit has been shown to correlate with vision-related quality of life.

**Discussion**

9.1.5. The Committee noted it reviewed the application for VN for the treatment of *RPE65*-IRD at its February 2023 meeting. At the February 2023 meeting, the Committee had concerns regarding:

- the durability of the gene expression and therefore the clinical effect
- the certainty regarding the number of people with *RPE65*-IRD in New Zealand
- if New Zealand had the appropriate compounding facilities and people with the appropriate skill set to deliver VN.

9.1.6. The Committee noted it had therefore deferred a recommendation in February 2023 until further evidence regarding the durability/longevity of the therapeutic benefits became available.

9.1.7. The Committee noted in making this recommendation that data from subsequent follow-up from the Phase 3 trial cohort, and emerging evidence around treatment effect for gene therapies more generally, would provide greater confidence on the expected duration of the health benefits associated with individuals being treated with voretigene neparvovec.

9.1.8. The Committee noted correspondence from the supplier and an ophthalmologist in New Zealand had been provided to address the Committee's concerns.

9.1.9. The Committee noted Pharmac sought advice from the Ophthalmology Advisory Committee at its August 2024 meeting, regarding concerns raised by PTAC in February 2023. The Committee noted that at the time of the 16 August 2024 meeting finalised records of the Ophthalmology Advisory Committee's discussion were not available.

However, in summary, following review of the funding application and the supplier and clinician correspondence, the Ophthalmology Advisory Committee had considered there was sufficient evidence addressing PTAC's concerns and had recommended that VN be listed with a high priority (within the context of treatment of eye diseases).

9.1.10. The Committee noted the clinician correspondence reporting that a clinical centre in Auckland has the appropriate facilities for compounding VN, the specialised clinicians to deliver VN, and has a database of genetic ophthalmic conditions which reports there are three people with *RPE65*-IRD in New Zealand. The Committee noted the Ophthalmology Advisory Committee considered this clinical centre to be the most appropriate place to deliver treatment and felt confident that the database of genetic ophthalmic conditions would accurately enumerate the number of people with *RPE65*-IRD in New Zealand.

9.1.11. The Committee noted that VN delivers the functional *RPE65* gene as an episome to the retinal cells using an adeno-associated virus (AAV) vector. As the gene does not integrate into the cell genome, there are concerns regarding the persistence of the functional gene, and therefore benefit, following cell division for the person. The committee noted that as photoreceptors are non-dividing cells there is reasonable biological plausibility of persistence of the episome in these cells.

9.1.12. The Committee noted the Marco et al. Mol Ther Methods Clin Dev. 2021;23:370-89 study, which reported that at the seven year follow-up, the encoded therapeutic proteins continued to persist following an AAV-based gene transfer to the central nervous system.

9.1.13. The Committee noted the Greig et al. Nat Biotechnol. 2024;42:1232-42 study, which reported the integration of the AAV vector sequence in every 1:100 non-human primate hepatocytes.

9.1.14. The Committee noted Leroy et al. Ophthalmic Res. 2023;66:179-196, which reviewed long-term follow-up data from the phase one and three trials, reporting up to 7.5 and 5 years, respectively. The Committee noted that at the 7.5-year follow-up, the improvements in the full-field light sensitivity threshold (FST) persisted (n=4). The Committee considered in light of the small sample size, this data may represent stable RPE65 transfection and persisting benefit; or it may represent a declining benefit with time. The Committee considered it to be uncertain at this time.

9.1.15. The Committee noted Fischer et al. Biomolecules.2024:122, which reported the two-year follow-up data from the PERCEIVE study. The mean change (SD) from baseline in FST was numerically higher in people aged <18 years (year 1 -29.80 [SD 1.28, n=2]; year 2 -17.12 [SD 18.44, n=3]) compared to those aged ≥18 years (year 1 -12.35 [SD 13.64, n=8], year 2 -12.63 [SD 24.5, n=10]). The Committee noted there is a wide range of therapeutic effects as the error bars go through zero. The Committee considered that the therapeutic effect may wane with time; however, considering the evidence is of low quality this is uncertain.

9.1.16. The Committee considered there to be both direct patient evidence and biological precedence to suggest that the functional *RPE65* gene will continue to persist within the retinal cells and provide clinical benefit to some patients with *RPE65*-IRD for longer than 7 years. The Committee considered that the persistence of a therapeutic effect may be better in people under the age of 18 years, as there may be more residual viable photoreceptor cells at the time of treatment, but the differential effect is, as yet, not unequivocally proven.

9.1.17. The Committee considered that even a relatively short period of maintenance of vision could have a positive lifelong impact, for example if it allows the person to complete formal education.

9.1.18. The Committee considered that due to the progressive nature of the disease, retinal cells would continue to be damaged and degenerate without intervention. The Committee noted that in the proposed Special Authority criteria, a person would be eligible if they have sufficient viable photoreceptor cells. The Committee noted there will

be variability and subjectivity regarding what is considered to be a sufficient number of cells. The Committee requested Pharmac seek advice from clinicians and the supplier regarding the definition of sufficient number of viable photoreceptor cells.

9.1.19. The Committee noted the Maguire et al. Ophthalmology. 2019;126:1273-85 study, which reported a post-hoc analysis demonstrating a Pearsons correlation coefficient of -0.71 between change in bilateral multi-luminance mobility test and change in FST average in both eyes. The Committee considered FST to be an appropriate surrogate marker of treatment benefit.

9.1.20. The Committee considered there would be substantial uncertainty regarding the cost-effectiveness of VN, largely due to the uncertainty regarding how long the treatment would last for. The Committee noted this uncertainty was also reported by other Health Technology Assessment agencies (CADTH and NICE).

9.1.21. The Committee noted any modelled benefits would have been considered in time periods beyond where clinical data are currently available. The Committee noted that different timeframes have been modelled by other Health Technology Assessment agencies and considered that a 10-year time horizon would be appropriate for modelling at this time.

9.1.22. The Committee noted the O'Brien et al. Clinicoecon Outcomes Res. 2023:15:29-39 study from the UK, which generated utility values for health states of varying levels of functional vision in retinitis pigmentosa, and considered this may be useful in Pharmac's economic assessment of VN.

9.1.23. The Committee considered, should individuals stop deriving benefit from voretigene neparvovec, further injections would not be given. The Committee considered this is because individuals who are no longer receiving benefit from VN treatment do so due to an immune response in the photoreceptor cells or continued macular degeneration/thinning and hence no further benefit would be derived.

9.1.24. The Committee indicated that, given the uncertainty regarding the duration of benefit, they were supportive of Pharmac staff exploring funding options that share financial risk with the supplier, and noted that full field light sensitivity could be an appropriate measure for any outcome-based funding.

*Summary for assessment*

9.1.25. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for VN if it were to be funded in New Zealand for RPE65-IRD. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | |
|---|---|
| Population | People with inherited retinal dystrophy due to pathological biallelic mutations of the *RPE65* gene, with sufficient viable retinal cells. |
| Intervention | Voretigene neparvovec, administered once as a subretinal injection in each eye in combination with peri-procedural treatment with prednisone. |
| Comparator(s) | Best supportive care |
| Outcome(s) | Improved multi-luminance mobility testing (MLMT)<br>• Russell et al. Lancet. 2017;390:849-60 reported that voretigene neparvovec treatment is associated with improvement in MLMT score compared to placebo. The mean bilateral MLMT change score was 1·8 (SD 1·1) light levels in the intervention group versus 0·2 (1·0) in the control group (difference of 1·6, 95% CI 0·72–2·41, p=0·0013).Further, 13 (65%) of 20 intervention participants, but no control participants, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement.<br>Improved vision<br>• Russell et al. 2017 reported that voretigene neparvovec treatment is associated with an improvement in LogMAR score compared to placebo at 1-year post-treatment (mean difference -0.16, 95% CI = -0.41 to 0.08).<br>• The long-term duration of such benefits is uncertain<br>Reduced vision impairment (ie nimproved LogMAR score) is associated with improvements in health-related quality of life (Lloyd et al. BMJ. 2019;103:1610-14). |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 9.2. Assessment advice: Multivitamins with trace elements for bariatric surgery – to confirm approach to economic modelling

### Application

9.2.1. The Committee reviewed the proposed approach to an economic assessment for multivitamins with trace elements in the prevention of micronutrient deficiencies in people who have undergone bariatric surgery for obesity.

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

### Discussion

*Māori impact*

9.2.3. The Committee discussed the impact of funding multivitamins with trace elements for the prevention of micronutrient deficiencies in people after bariatric surgery on Pharmac | Te Pātaka Whaioranga's Hauroa Arotahi | Māori health areas of focus and Māori health outcomes.

9.2.4. The Committee noted that severe obesity can materially affect, contribute to or be affected by at least four of the five Hauora Arotahi (hauora hinengaro | mental health; matehuka | diabetes; manawa ora | heart health-high blood pressure & stroke; romaha ora | respiratory health; mate pukupuku | cancer – lung cancer and breast cancer).

9.2.5. The Committee noted that Māori are among those who experience high rates of obesity but that they currently have lower rates of publicly-funded bariatric surgery, with them receiving very low rates of bariatric surgery in the private sector. The Committee considered that Māori were substantially affected by inequities in this context.

*Populations with high health needs*

9.2.6. The Committee discussed the health need(s) of people following bariatric surgery among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027

to have high health needs. The Committee discussed the impact of funding multivitamins with trace elements and noted that, alongside Māori (see previous section), Pacific people, people with disabilities, those living in rural areas, and those living in areas of socioeconomic deprivation also experienced substantial inequities in access to bariatric surgery, relating to factors including geographic location and access otherwise to health services that meet all needs. The Committee considered that the health outcomes of these groups would also be impacted by variable follow-up practices.

9.2.7. The Committee considered this is an important area for improvement that would require cross-agency collaboration.

*Background*

9.2.8. The Committee noted that in 2015, Pharmac received an application to fund multivitamins with trace elements for the prevention of micronutrient deficiencies in patients before/after bariatric surgery. The application was supported by the Bariatric Service at Capital Coast DHB, Dietitians NZ Bariatric Special Interest Group (SIG), and the Dietitians Leadership Group.

9.2.9. The Committee noted that the application proposed a number of vitamin preparations as options for funding, including Centrum 50+, Nutrichew by BandBuddies, Clinicians Multivitamin and mineral foods, and Celebrate Multivitamin chews.

9.2.10. The Committee noted that in October 2018 the application was reviewed by the Gastrointestinal Subcommittee (now Advisory Committee), which recommended it be funded with a high priority, in the context of gastrointestinal treatments, based on the unmet need for adequate micronutrient supplementation among people who have undergone bariatric surgery. At that time:

9.2.10.1. The Subcommittee noted that whilst there is adequate evidence to demonstrate that patients who undergo bariatric surgery often experience nutrient deficiencies, there was little evidence that supplementation improves patient outcomes.

9.2.10.2. The Subcommittee noted that the currently funded multivitamin, Mvite (which is funded without restrictions), does not contain adequate micronutrients or trace elements, and considered that none of the other products in the application provided suitable levels of supplementation for people who have undergone bariatric surgery. The Subcommittee recommended that a more complete multivitamin/trace element preparation be sought for funding.

9.2.11. The Committee noted that in February 2019, PTAC noted and accepted the Subcommittee's recommendation for multivitamins with trace elements.

9.2.12. The Committee noted that Pharmac staff received advice in 2024 from bariatric specialist dietitians about the suitability of multivitamin preparations currently available in New Zealand that could feasibly be funded and about several areas of uncertainty in the economic assessment. The Committee noted that Pharmac staff sought advice from the Committee on these.

*Health need*

9.2.13. The Committee noted that New Zealand has one of the highest rates of obesity among countries in the Organisation for Economic Co-operation and Development (OECD), with one in three adults classified as obese and higher rates of obesity among Māori, Pacific people, disabled people and those living in areas with high socioeconomic deprivation (Ministry of Health – Obesity statistics).

9.2.14. The Committee noted that bariatric surgery is used as treatment for obesity if patients meet certain criteria, and the different procedure types can be broadly categorised as restrictive surgery, malabsorptive surgery, or both. Restrictive surgery comprises approximately 62% of bariatric operations in New Zealand and includes sleeve gastrectomy (the most common), endoscopic gastric balloon inflation, and gastric

banding (which is now used less frequently in New Zealand). Malabsorptive surgery is undertaken in approximately 38% of cases and includes gastric bypass surgery and biliopancreatic diversion with duodenal switch (Garrett et al. Obes Surg. 2020;30:2285-93). This surgery is available to people with a body mass index (BMI) over 35 with co-morbidities, or BMI over 40 without co-morbidities.

9.2.15. The Committee noted that this application did not target people undergoing the same type of surgery for other reasons apart from weight loss, but considered it could be appropriate to include such people simply by referring to surgery type. The Committee considered that outcomes from multivitamin supplementation would be similar for people undergoing the same surgical operations for other indications, and that including these individuals in this assessment would increase the size of the group by a small number of people.

9.2.16. The Committee noted that there are geographic differences in the type of surgery and number of bariatric operations undertaken across New Zealand, and that Māori and Pacific are less likely to undergo such surgery (Garrett et al. 2020). The Committee noted a longitudinal follow-up study of a cohort of 328,739 New Zealanders aged 30–79 years with obesity who had received cardiovascular risk assessment in primary care between 2010 and 2018 (Bennett et al. Surg Obes Relat Dis. 2021;17:1286-93), which reported Māori or Pacific people were less likely to receive bariatric surgery than non-Māori, non-Pacific people (adjusted hazard ratios 0.82 [95% CI 0.69, 0.96] and 0.24 [0.20, 0.29], respectively) and the likelihood of receiving publicly funded surgery varied inversely with increasing socioeconomic deprivation and rurality.

9.2.17. The Committee noted data published in 2020 on bariatric surgery in New Zealand between 2004-2017 (Garrett et al. 2020). The Committee noted that the number of bariatric operations performed privately had increased over time, with more than half performed privately, and considered that an additional group of people travel overseas to self-fund their surgery at a lower cost. The Committee noted Garrett et al. reported that more than 80% of private bariatric operations were in Europeans, 12% in Māori, and almost none in Pacific people (1.9%), while 24% and 9% of public bariatric operations were performed for Māori or Pacific people, respectively (Garrett et al. 2020).

9.2.18. The Committee expressed concern regarding the inequity of access to bariatric surgery in New Zealand and further noted that follow-up practices can be variable. Members noted that, one to two years after bariatric surgery, patient care transitions from bariatric specialist services to their GP. The Committee noted that people who have undergone bariatric surgery may face unique challenges in non-specialist healthcare settings that may negatively impact their health experiences, potentially resulting in lower attendance at monitoring visits.

9.2.19. The Committee noted that following bariatric surgery, people can have insufficient levels of various micronutrients, notably vitamin B12, thiamine, iron and vitamin D. The Committee noted that there is no data on current multivitamin and trace element use by bariatric surgery patients in New Zealand, and that VitABDECK and MVite are not suitable options due to their low vitamin content and because they do not contain any trace elements. The Committee considered that VitABDECK or Mvite could theoretically be prescribed by non-bariatric specialists, however, that the majority of people receiving multivitamins after bariatric surgery would either self-fund bariatric or standard multivitamin preparations, or be unable to adhere to any prescribed multivitamin treatment sufficiently to receive optimal benefits.

9.2.20. The Committee noted anecdotal evidence that pre-operative screening processes for bariatric surgery in some places included consideration of a person's ability to self-fund supplements post-surgery, although members considered this was not a barrier to receiving bariatric surgery.

*Multivitamin preparations*

9.2.21. The Committee noted that since 2023, some bariatric multivitamin preparations are no longer available in New Zealand due to exceeding doses outlined in Medsafe's dietary

supplement regulations. The Committee noted that this limits the availability of bariatric multivitamins in New Zealand, and that the available preparations might not completely meet the needs of people who have undergone bariatric surgery in New Zealand.

9.2.22. The Committee noted that three multivitamin brands (BN, TRIC, BariLife) were recommended by the Dietitians New Zealand Bariatric Special Interest Group (SIG), who suggested dosing for four sub-populations according to the type of bariatric surgery.

9.2.23. The Committee noted that BariLife is not available in New Zealand and therefore it was not considered in detail at this time. The Committee noted that BN chews and capsules met or exceeded the recommended daily intake (100% RDI) for all vitamins and trace elements except copper (which is important to supplement diets in New Zealand), but considered that patients who have undergone bariatric surgery often require higher vitamin doses.

9.2.24. The Committee noted that the Dietitians New Zealand Bariatric SIG recommended that ideally more than one multivitamin option should be made available so that acceptability is not limited, adherence is maximised, and to enable availability of iron and non-iron containing options.

*Health benefit*

9.2.25. The Committee noted that the suggested multivitamin preparations by BN and TRIC have not been assessed in comparative clinical trials.

9.2.26. The Committee noted and reviewed two randomised controlled trials (RCTs) investigating two multivitamin preparations which contained a wide range of vitamins and trace elements – WLS Optimum 1.0 (Heusschen et al. Obes Surg. 2020;30:1280-90) and WLS Forte (Dogan et al. Medicine (Baltimore). 2014;93:e169).

9.2.27. The Committee noted that the multivitamins assessed in the two RCTs contained lower doses of some vitamins (particularly thiamine) than the optimum quantities advised for bariatric surgery patients in New Zealand, but considered these preparations provided a wider range of multivitamins and trace elements than Mvite and VitABDECK.

9.2.28. The Committee noted that the RCTs involved a small number of people and that outcomes were focused more on detecting serological deficiencies than on clinical consequences, which would require a longer period of follow-up. However, the Committee considered it reasonable to infer that optimal nutrient levels would convey health benefits. The Committee considered that the beneficial effects of multivitamins on anaemia, the B vitamins and vitamin D were the most relevant for New Zealand people who have undergone bariatric surgery.

9.2.29. The Committee agreed with the Dietitians New Zealand Bariatric SIG suggestion that BN and TRIC multivitamins can probably be considered at least as effective as the preparations assessed in the RCTs and would be appropriate multivitamins to fund for this population, although noted that vitamin B12 and folate levels are lower in the BN and TRIC multivitamins than in the preparations assessed in the trials.

9.2.30. The Committee also noted the following extension studies and retrospective analyses assessing the impact of WLS Optimum and WLS Forte:

- Heusschen et al. Obes Surg. 2021;31:2520-8
- Heusschen et al. Obes Surg. 2022;32:3561-70
- Homan et al. Surg Obes Relat Dis. 2016;12:659-67
- Smelt et al. Obes Surg. 2020;30:427-38
- Schijns et al. Obes Surg. 2018;14:1005-12.

9.2.31. The Committee considered that the retrospective and extension studies were of low quality, were affected by low adherence rates, and had some crossover in the extension studies. The Committee noted that the proportions of surgical approaches and baseline vitamin deficiencies in New Zealand may differ from those of individuals from other

countries participating in the studies (eg selenium deficiencies tend to be more frequent in New Zealand, whereas the studies were mostly conducted in The Netherlands).

9.2.32. The Committee considered that funding a chewable product for the first three months post-surgery, followed by a tablet or capsule formulation thereafter, was reasonable. The Committee did not identify any other bariatric multivitamin option that was any more appropriate to consider.

*Suitability*

9.2.33. The Committee noted that the Dietitians Group had recommended that:

- More than one option be available so that acceptability is not limited and adherence is maximised.
- A chewable product funded for the first three months following surgery.
- Both iron and non-iron containing options be available, given that not all people would require or tolerate iron supplementation.

9.2.34. The Committee considered that BN and TRIC are appropriate options for nutritional content and suitability. It was noted that BN has the advantage that it is available in a chewable and capsule formulation, and TRIC has the advantage of having a higher fat-soluble vitamin content and includes an iron-free option. The Committee agreed that more than one preparation is required, and that this includes having a chewable product funded for the first three months following surgery.

9.2.35. The Committee considered that longterm prescribing would be appropriate and that patient and prescriber education would be required to support longterm use.

*Costs and savings*

9.2.36. The Committee considered that additional health sector costs associated with monitoring for deficiencies may be incurred, as none of the bariatric multivitamin preparations fully meet the required quantities.

*Summary for assessment*

9.2.37. The Committee noted the planned approach for the economic assessment proposed by Pharmac staff. The Committee considered that it is reasonable to assume that any pre-existing micronutrient deficiencies are addressed prior to surgery.

9.2.38. The Committee discussed the comparator in the proposed assessment and agreed that it should be 'no multivitamin treatment', given funded multivitamins (VitABDECK and MVite) are not suitable and patients who are taking supplements are predominantly self-funding their treatment at the moment. The Committee considered that VitABDECK could possibly be included as comparator for ~10% of the population (ie a third of those who would have malabsorptive surgery), but that the benefit derived from VitABDECK supplementation will be highly uncertain.

9.2.39. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for multivitamins with trace elements if it were to be funded in New Zealand for the prevention of micronutrient deficiencies in patients who have undergone bariatric surgery. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | |
|---|---|
| **P**opulation | People who have undergone bariatric surgery.<br>Two subgroups have been identified based on the type of bariatric surgery received. People in these two groups are anticipated to have differing supplementation needs (in relation to vitamin dose requirements) and outcomes (in relation to likelihood of complications due to malabsorption issues). |

| | | |
|---|---|---|
| | Restrictive surgery includes gastric banding or sleeve gastrectomy.<br>Estimated to be around 62% of all bariatric operations in New Zealand (Garrett et al 2020). | Malabsorptive surgeries include gastric bypass or biliopancreatic diversion with duodenal switch.<br>Estimated to be around 38% of all bariatric operations in New Zealand (Garrett et al 2020).<br>*Includes operations considered both malabsorptive and restrictive.* |
| **I**ntervention | Intervention options suggested by Dietitians NZ Bariatric SIG.<br>Supplement should be in liquid, powder or chewable form immediately post bariatric surgery for 3 months, then capsule or tablet version thereafter.<br>Recommended that people stay on supplements for life. However, adherence to multivitamins is a significant issue. | |
| | - BN chews (month 1-3) followed by BN caps<br>OR<br>- BN chews (month 1-3) followed by TRIC multivitamin (preparations with or without iron)<br>Some people will require additional iron. | - BN chews (month 1-3) followed by BN caps<br>OR<br>- BN chews (month 1-3) followed by TRIC multivitamin (preparations with or without iron)<br>All people will require additional calcium and Vitamin D. Some individuals will require additional iron and VitABDECK. |
| **C**omparator(s) | No multivitamin | No multivitamin (majority of people)<br><br>Some people (approx. ~10% of total eligible population) might be eligible for VitaBDECK based on clinical advice received from Dietitians New Zealand SIG. Assume these individuals will also require additional iron, calcium and Vit D. |
| **O**utcome(s) | ○ Decrease in new nutrient (or nutrient-related) deficiencies, specifically:<br>○ Ferritin<br>○ Vit B12<br>○ Folate<br>○ Anaemia<br>○ Vitamin D<br><br>*Note: Reduction in iron, Vit B12 and folic acid deficiencies were selected as the main treatment outcomes, as differences in these deficiencies can potentially be adequately addressed through multivitamin use, and these deficiencies are reported frequently in the published scientific literature.* | |

*Table definitions:*

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

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

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

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

## 10. Ferric carboxymaltose – people with hereditary haemorrhagic telangiectasia where serum ferritin is ≤50 mcg/L or transferrin saturation is ≤20%

### Application

10.1. The Committee reviewed the applications for widening access to ferric carboxymaltose (Ferinject) for people with hereditary haemorrhagic telangiectasia (HHT) where serum ferritin is ≤50 mcg/L or transferrin saturation is ≤20%. The Committee noted that members of the HHT support group were engaged with Pharmac staff throughout the application process and acknowledged the applicants had provided comprehensive applications.

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

**Recommendation**

10.3. The Committee **recommended** that the applications for widening access to ferric carboxymaltose for people with HHT with serum ferritin ≤50 mcg/L or transferrin saturation ≤20% be **declined**.

10.4. In making this recommendation, the Committee:

10.4.1. Recognised the high health need of people with HHT and especially the unmet need due to chronic iron deficiency and challenges with timely access to a suitable iron replacement product.

10.4.2. Noted that the evidence base in HHT is limited, as expected for a relatively rare disease. However, the Committee, considered that there was insufficient evidence (in this disease and extrapolated from other indications) of significant clinical benefits from changing the threshold to access ferric carboxymaltose as proposed.

10.4.3. Noted the increased risk of hypophosphatemia where ferric carboxymaltose is used repeatedly and considered there was poor awareness of this safety concern among New Zealand clinicians prescribing ferric carboxymaltose.

10.4.4. Noted that the hypophosphatemia risk is the reason that international treatment guidelines for HHT do not recommend repeated use of ferric carboxymaltose in this disease, and instead recommend other iron products be used where available.

10.4.5. Considered that a different intravenous (IV) iron product may more appropriately address the unmet health need of people with HHT with iron deficiency.

10.5. The Committee considered that Pharmac should encourage funding application(s) for other IV iron treatment(s) with better safety profiles and accompanied by evidence of benefit if available, noting that HHT clinical management guidelines list several iron products considered by experts to be suitable for use in the disease.

10.6. The Committee considered that Pharmac should consider engaging with health sector partners such as the Goodfellow Unit to increase prescriber awareness of the hypophosphatemia risk and management with repeat infusions of ferric carboxymaltose.

**Discussion**

*Māori impact*

10.7. The Committee discussed the impact of widening access to ferric carboxymaltose for people with hereditary haemorrhagic telangiectasia (HHT) as proposed on Pharmac | Te Pātaka Whaioranga's Hauroa Arotahi | Māori health areas of focus and Māori health outcomes. The Committee was not aware of any increased health impact from HHT in Māori compared with non-Māori, but considered Māori with HHT may be affected more than non-Māori as they are more likely to live in rural or socioeconomically deprived areas, affecting access to specialist care and intravenous infusion service (see section below).

*Populations with high health needs*

10.8. The Committee discussed the health need(s) of people with HHT among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding ferric carboxymaltose and considered that people living in rural or socioeconomically deprived areas can experience barriers to accessing specialist care (e.g. the ability to get a referral, referral acceptance and availability of specialists, distance from home for specialist visits) and challenges associated with accessing ferric carboxymaltose infusion (e.g. the steps involved in arranging the infusion and payment for its administration, which is variable around the country). The Committee considered that for those with HHT with iron deficiency, these access issues may result in worse health outcomes.

10.9. The Committee considered that its main concern about inequity related to the likely substantial underdiagnosis of HHT in New Zealand and particularly amongst populations that face additional barriers when accessing the health system.

10.10. The Committee was made aware of evidence from the UK indicating that greater HHT diagnosis rates occurred in economically affluent populations compared with less affluent populations (Donaldson et al. Thorax. 2014;69:161-7). The Committee considered that if this were extrapolated to the New Zealand context, funding a treatment for people diagnosed with HHT, who are more likely to be affluent, could worsen existing health and access inequities.

*Background*

10.11. The Committee noted that ferric carboxymaltose (Ferinject) is funded for hospital use (restricted to cases where treatment with oral iron has proven ineffective or is clinically inappropriate) and in the community subject to Special Authority criteria for iron deficiency anaemia (a low haemoglobin associated with iron deficiency) where serum ferritin is ≤20 mcg/L in people for whom oral iron has either been ineffective or intolerable.

10.12. The Committee noted that a proposal to widen access to ferric carboxymaltose in the community has been considered for iron deficiency anaemia in patients with an inflammatory response, serum ferritin of 20 mcg/L to 50 mcg/L and CRP >5. It was ranked on the Options For Investment list and is currently included in a public consultation regarding a number of proposals to fund or widen access to medicines.

10.13. The Committee noted that the current applications propose ferric carboxymaltose be funded for those with HHT with iron deficiency without anaemia, where serum ferritin is ≤50 mcg/L, or where transferrin saturation is ≤20% in cases with ferritin over 50 mcg/L due to an inflammatory state. The Committee considered this request to widen the currently funded access would be an incremental change for this population.

10.14. The Committee noted that the applicants had expressed their interest in submitting funding applications in future for an alternative IV iron product and bevacizumab for HHT.

*Health need*

10.15. The Committee noted that HHT is an autosomal dominant disease resulting in vascular abnormalities (arteriovenous malformations or AVMs) affecting several organ systems. The Committee noted that typical signs of HHT are severe spontaneous nosebleeds in early life and that, as an individual ages, small AVMs or telangiectasias occur in the skin and mucous membranes, while large AVMs develop in the lungs (occurring in about 60% of cases), liver or brain (Hammill et al. Hematology Am Soc Hematol Educ Program. 2021;2021:469-77). The Committee noted that symptomatic liver AVMs, gastrointestinal bleeding, and anaemia are associated with reduced life expectancy in HHT and pulmonary AVMs are associated with ischaemic stroke (Al-Samkari. Blood. 2021;137:888-

95; Kasthuri et al. Am J Hematol. 2017;92:E591-625; Shovlin et al. Plos One. 2014;9:e88812; Shovlin C. A J Resp and Crit Care Med; 2014:190:1217-88).).

10.16. The Committee noted that the reduction in quality of life for people with HHT across most domains is similar to that reported in other chronic diseases (Geirdal et al. Am J Med Genet A. 2012;158A:1269-78; Geisthoff et al. Otolaryngol Head Neck Surg. 2007;136:726-33; discussion 734-5; Ingrand et al. Rhinology. 2011;49:155-62; Merlo et al. Int Forum Allergy Rhinol. 2014;4:921-5; Pasculli et al. Qual Life Res. 2004;13:1715-23; Zarrabeitia et al. Health Qual Life Outcomes. 2017;15:19). The Committee further noted the impact to an individual of fatigue in iron deficiency without anaemia, and the impact on quality of life and healthcare costs associated with ischaemic stroke.

10.17. The Committee noted that the clinician applicant estimates that about 104 people in New Zealand have been diagnosed with HHT (10% diagnosed out of about 1,044 people with HHT), based on low rates of diagnosis internationally and a reported prevalence of 1 in 5,000 per population (Kjeldsen et al. J Int Med. 1999;245:31-9). The Committee considered that 10-20% was a reasonable estimate for the proportion of those with HHT who are diagnosed in New Zealand and was made aware of US and UK evidence suggesting a diagnosed prevalence of 0.15 to 0.21 per 5000 or 1 in 9400 (Saparia et al. Perm J. 2019:23:18-145; Grosse et al. Genet Med. 2014;16:33-9; Donaldson et al. Thorax. 2014;69:161-7).

10.18. The Committee further considered that low diagnosis rates consequently represented an issue for undiagnosed people with HHT who would not be accessing monitoring and treatment for HHT manifestations. The Committee considered that those diagnosed were more likely to be older and experiencing a greater burden of symptoms of the disease. The Committee noted that a range of clinicians would diagnose and manage HHT.

10.19. The Committee noted that HHT has a spectrum of disease severity with about 40% experiencing mild bleeding, 40% moderate bleeding and 20% severe bleeding. The Committee noted that very severe disease leading to blood transfusion dependency occurs in approximately 5% of those with severe disease (Al-Samkari. Blood. 2024;144:940-54). The Committee noted that, in general, people with HHT frequently need medical care to manage disease manifestations, and those who experience chronic blood loss and iron deficiency have a high health need. The Committee was made aware of data indicating that younger people with HHT are less likely to be anaemic and that the proportion who are anaemic increases from about the age of 60 years (Kasthuri et al. Am J Hematol. 2017;92:e591-e593).

10.20. The Committee noted that iron supplementation is a supportive care approach in HHT rather than a treatment for the underlying cause of bleeding, and noted expert opinion regarding management of HHT is to maintain a normal haemoglobin with ferritin of at least 50 mcg/L and transferrin saturation of at least 20% (Al-Samkari. 2024).

10.21. The Committee noted that iron deficiency treatment for people with HHT in New Zealand can vary depending on the treating clinician/specialist, health system access, and geographic location. The Committee noted there are issues accessing IV iron treatments especially for those living in rural areas or with other barriers such as challenges accessing specialist care. The Committee noted that some iron infusions occur in an acute setting (e.g. post red blood cell [RBC] transfusion) but consider there would be some regional variation. The Committee considered that iron infusion may occur post-RBC transfusion only in an initial instance unless an individual was transfusion dependent.

10.22. The Committee noted there is an increased risk of hypophosphatemia associated with repeated use of ferric carboxymaltose. The Committee noted that hypophosphatemia can lead to serious consequences such as osteomalacia and bone fractures, and considered this a major safety concern in the setting of repeat infusions in HHT (van Doren et al. Am J Hematol. 2024;99:1338-48; Medsafe Data Sheet, TGA (Australia) Product Information,

FDA Prescribing Information (label)). The Committee was made aware that higher rates of hypophosphatemia have been reported in other indications, for example a study in people with iron deficiency anaemia due to inflammatory bowel disease where hypophosphatemia was reported in 51% who received ferric carboxymaltose compared with 8.3% who received iron derisomaltose (Zoller et al. Gut. 2023;72:644-53). Members noted that some studies investigating hypophosphatemia incidence were funded by sponsors of other iron products and thus the publications may have bias.

10.23. The Committee noted several clinical and consensus guidelines, policy statements and reviews of management for HHT, some of which specifically advise caution or avoidance of ferric carboxymaltose in HHT where there are other iron options available, due to the hypophosphatemia risk (CureHHT Policy statement. HHT Foundation International, Inc. June 2021; Faughnan et al. Ann Intern Med. 2020;173:989-1001; McDonald et al. 2000 [Updated 2021 Nov 24]. GeneReviews [Internet]; van Doren et al. Am J Hematol. 2024;99:1338-48; Al-Samkari. 2021; Garg et al. J Blood Med. 2014;5:191-206; Hammill et al. Am Soc Hematol Educ Program. 2021:469-77; Al-Samkari. 2024).

10.24. The Committee considered there to be a low level of awareness among New Zealand prescribers of the increased risk of hypophosphatemia with repeat infusions of ferric carboxymaltose for iron deficiency anaemia in general, which was also a concern.

*Health benefit*

10.25. The Committee noted the that the applicants considered that widening access for people with HHT with iron deficiency may reduce the risk of ischaemic stroke, fatigue, requirements for red blood cell (RBC) transfusions, speed and volume of alloantibody development, and health system resource use. The Committee noted that HHT is a relatively rare condition and that the evidence base mostly consists of expert opinion with an expected scarcity of large, robust, clinical trial evidence investigating these outcomes. The Committee considered that, to assess the potential benefits of changing the threshold to access ferric carboxymaltose based on a higher ferritin level of ≤50 mcg/L or transferrin saturation of ≤20%, it was appropriate to consider extrapolating evidence from other health states without anaemia where it is used for iron repletion.

10.26. The Committee noted the following evidence in people with HHT:

10.26.1. A study of 497 people with HHT with CT-proven pulmonary AVMs reported that 61 (12.3%) had ischaemic strokes and there was an association between stroke and low serum iron (adjusted odds ratio 0.96; 95% confidence interval 0.92, 1.00) (Shovlin et al. 2014). The Committee considered that as the upper confidence interval reaches 1, there is uncertainty in this association and considered this inconclusive on whether low serum iron is predictive of ischaemic stroke in HHT.

10.26.2. In the same publication, the authors reported numerically similar median baseline values in the no stroke and ischaemic stroke groups, respectively, for serum iron (12 µmol/L no stroke, 9 µmol/L ischaemic stroke; *P*=0.025), ferritin (29.5 mcg/L no stroke, 34.5 mcg/L ischaemic stroke; *P*=0.55), and haemoglobin (14.2 g/dL no stroke, 13.8 g/dL ischaemic stroke; *P*=0.25). The Committee noted the authors also reported an association between pulmonary AVMs and individuals being twice as likely to have arterial thrombosis and 2.5 times more likely to have venous thrombosis. Members noted that those with more severe HHT were more likely to have iron deficiency and were also more likely to have those associations.

10.26.3. A study reporting an association between deep vein thrombosis (DVT) or pulmonary embolism (PE) and low serum iron, with iron deficiency causing elevated factor VIII levels and thus being associated with increased risk of DVT or PE (Livesey et al. Thorax. 2012;67:328-33). The Committee noted that the association was with serum iron rather than ferritin, and that this was in the presence of anaemia.

10.26.4. A study investigating the frequency of basal ganglia manganese deposit-induced lesions (BGMnIL) in people with HHT and the relationship between these lesions, iron deficiency anaemia and hepatic vascular malformations (HVMs) (Serra et al. Orphanet J Rare Dis. 2017;12:92). The Committee noted that the risk of having lesions was higher in the presence of iron deficiency anaemia in those with HVMs (odds ratio 7.73; 95% CI: 2.23, 26.73). However, the Committee noted that serum ferritin levels were low in both groups (14.1 ng/mL BGMnIL, 22 ng/mL non-BGmnIL; *P*=0.004) and that while the odds ratio was subsequently adjusted for age, there was a large age difference between the BGMnIL and non-BGMnIL groups. The Committee considered that this was a biologically plausible association between anaemia and manganese deposit-induced lesions that required caution in its interpretation.

10.27. The Committee was made aware of evidence from systematic reviews of randomised controlled trials across multiple clinical indications, which each concluded that iron infusions reduce the number of red blood cell transfusions and number of units transfused (Litton et al. BMJ. 2013:347:f4822; Shah et al. JAMA Netw Open. 2021;4:e2133935). The Committee noted the risks of serious complications from blood transfusions including the rare risk of developing alloantibodies and considered that avoiding transfusions is advantageous for reasons including reduction of these risks. The Committee noted that no direct evidence would be expected but considered that maintaining an iron replete state for people with HHT who have chronic bleeding would be anticipated to decrease the requirements for blood transfusions, although the magnitude of this decrease was unknown.

10.28. The Committee noted clinician input on a submission to the Canadian CADTH that described evidence of greater mortality in people with heart failure with iron deficiency, and American treatment guidelines that recommend IV iron treatment commences for iron deficiency in this population irrespective of the presence of anaemia.

10.29. The Committee was made aware of the following evidence for the impact of iron treatment on fatigue in other health states with iron deficiency without anaemia:

10.29.1. A double-blind randomised controlled trial investigating the impact of IV iron (hydroxide sucrose) vs placebo on fatigue in 90 premenopausal women with iron deficiency without anaemia (Krayenbuehl et al. Blood. 2011;118:3222-7). A clinically meaningful decrease in fatigue occurred only in those with serum ferritin of ≤15 mcg/L and/or transferrin saturation ≤20%. The Committee considered that these results do not suggest a ferritin threshold change from 20 mcg/L to 50 mcg/L would have a different impact on fatigue.

10.29.2. A meta-analysis of cross-sectional studies and randomised controlled trials investigating iron for iron deficiency without anaemia (Yokoi et al. Br J Nutr. 2017;117:1422-31). The Committee considered that this evidence indicates a benefit from iron supplementation for fatigue, however, the magnitude of benefit and clinically meaningful level of improvement remain unclear in the face of mixed quality of evidence.

10.30. The Committee acknowledged that maintaining an iron replete state for people with HHT may prevent some individuals from experiencing severe impacts of the disease such as anaemia and ischaemic stroke, when considering barriers to treatment access and variation in clinical presentation and bleeding rates. However, the Committee considered the evidence did not demonstrate statistically significant clinical benefits from ferric carboxymaltose for people with HHT with iron deficiency without anaemia. Specifically, the Committee considered that there was no evidence of a direct benefit in terms of reductions in the risk of stroke or fatigue from treatment with ferric carboxymaltose for iron deficiency with a ferritin threshold of 50 mcg/L compared with the current threshold of 20 mcg/L.

10.31. Overall, the Committee considered that the lack of evidence of benefit, in combination with the hypophosphatemia risk and clinical guidelines recommending caution or against repeated use of ferric carboxymaltose in HHT, made it difficult to support the request to change the threshold for access to ferric carboxymaltose for people with HHT.

*Suitability*

10.32. The Committee again noted that there is national variability in access, copayment structure and practice capacity in the community for provision of iron infusions. The Committee considered there is also variation in hospital approaches to IV iron infusion.

10.33. The Committee considered that, if access were widened as requested, phosphate levels would require monitoring; educational support would be needed for implementation; and access widening may be associated with a risk of complications of hypophosphatemia.

*Cost and savings*

10.34. The Committee considered that if an IV iron product were funded in the community for iron deficiency without anaemia in HHT, there may be a small rise in numbers in the first few years of funding, but HHT diagnoses would not substantially increase unless there was greater education. The Committee considered that the proportion of people with HHT that might have periods of life during which they may require frequent iron infusions (e.g. fortnightly) would be the 5-20% of HHT patients with severe bleeding.

10.35. The Committee considered that the frequency of IV iron use would vary due to differences in disease severity across the population with HHT in New Zealand and variable bleeding sites and rates over time in individuals. The Committee noted the applications reported infusions occurring as frequently as two-weekly for some, but considered this would be a small proportion requiring replenishment of low stores or massive ongoing bleeding in likely transfusion-dependent disease. The Committee considered that the time required for serum ferritin to reduce from 50 mcg/L to 20 mcg/L depends on the extent and speed of haemorrhage.

10.36. The Committee considered that the magnitude of any changes in health system resource use (eg reductions in acute presentations to Emergency Departments [ED] for blood transfusions) was unclear, based on a lack of evidence. The Committee considered that major bleeds would require an ED visit, although members noted that treatment with blood products and/or iron infusions may vary depending on hospital management and an individual's clinical state. The Committee considered it feasible that healthcare costs could be reduced if fewer people with HHT were becoming severely iron deficient.

10.37. The Committee considered that the evidence was insufficient to quantify cost offsets for blood transfusion and alloantibody rates but that it was intuitive that there would be some benefits and cost offsets, although the magnitude was highly uncertain.

## 11. Teriparatide – Osteoporosis, treatment for clinical vertebral fractures, 1st line

### Application

11.1. The Committee reviewed the application for teriparatide for the treatment of very high-risk osteoporosis.

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

### Recommendation

11.3. The Committee **recommended** that the listing of teriparatide in the Pharmaceutical Schedule be extended to the treatment of first line treatment of very high-risk osteoporosis, with a **low priority**, subject to the following Special Authority criteria:

Initial application from any relevant practitioner. Approvals valid for 18 months for applications meeting the following criteria:
All of the following
1. Either
    1.1. History of at least two fractures due to minimal trauma that are/were demonstrated radiologically; or
    1.2. The patient has had a vertebral fracture; and
2. Any of the following:
    2.1. Documented bone mineral density (BMD) T-Score less than or equal to -3.0, measured using dual-energy x-ray absorptiometry (DEXA); or
    2.2. The patient is aged 75 years or over; or
    2.3. Densitometry scanning (DEXA) cannot be performed because of major logistical, technical or pathophysiological reasons; or
    2.4. A 10-year risk of hip fracture greater than or equal to 4.5%, calculated using a published risk assessment algorithm (eg FRAX or Garvan) which incorporates BMD measurements, measured using DEXA scanning; and
3. The patient must not receive concomitant treatment with any other funded antiresorptive agent including denosumab; and
4. Treatment with teriparatide is not to extend beyond 18 months.

11.4. In making this recommendation, the Committee considered:

- people who are very high risk of a fragility fracture experience an unmet health need, due to the morbidity consequences associated with fragility fractures.
- publications discussed provided reasonably robust evidence to support the possibility that teriparatide is slightly more effective as a first-line agent for treating osteoporosis for people at very high risk of fragility fractures, particularly for reducing the risk of clinical vertebral fractures.
- people were more likely to choose oral or yearly infusion formulations over teriparatide's subcutaneous injections, where the Committee estimated that only 10% of eligible people would choose to have the daily teriparatide injections.
- the cost of teriparatide was higher than the cost of bisphosphonate therapy.

## Discussion

*Māori impact*

11.5. The Committee discussed the impact of funding teriparatide for the first line treatment of very high-risk osteoporosis on Māori health outcomes. The Committee noted osteoporosis is not one of Pharmac's five Hauora Arotahi | Māori Health Areas of Focus.

11.6. The Committee noted the proportion of Māori that were enumerated in the ANZFFR Annual Report 2024 who had a fragility fracture in 2022/23 was lower than expected for crude population prevalence. However, the Committee noted that this could well reflect crude incidence not accounting for the Māori population age structure being appreciably younger than the New Zealand European population structure (NZ Europeans being generally older, and where fragility facture risk rises markedly with age), and the consequent rate ratio was not age standardised.

*Populations with high health needs*

11.7. The Committee discussed the health need(s) of people with very high-risk osteoporosis among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding teriparatide for the first line treatment of very high-risk osteoporosis for people who have been underserved by the health system. As with Māori (see previous paragraph), the Committee did not identify any other groups with known inequitable health outcomes

associated with very high-risk osteoporosis, but noted that the lack of available evidence did not exclude the possible presence of such inequities.

11.8. The Committee noted the proportion of Pacific peoples that were enumerated in the ANZFFR Annual Report 2024 who had a fragility fracture in 2022/23 was lower than expected, but considered that this well could reflect crude incidence not accounting for the Pacific people population age structure being appreciably younger than the much older New Zealand European population.

*Background*

11.9. The Committee noted teriparatide is currently funded on Special Authority for people with severe established osteoporosis after receiving inadequate benefit from a funded anti-resorptive agent.

11.10. The Committee noted that in March 2021, the Endocrinology Specialist Advisory Committee (SAC) recommended that access to teriparatide be widened to first line; at that time, the SAC considered that teriparatide would provide significant health benefit for a small group of people with a clinical vertebral fracture, if used as a first line agent in severe osteoporosis. The Committee noted the SAC considered that bisphosphonates would then be used second line for these people. The Committee noted following this recommendation that it (PTAC) had considered this would be a substantial shift in clinical practice and suggested that the supporting evidence for this recommendation be reviewed.

*Health need*

11.11. The Committee noted osteoporosis is defined as either the presence of fragility fractures (fractures if the associated trauma would not have resulted in the fracture of a normal bone) in the absence of other metabolic bone disorders, with a normal bone mineral density (BMD) T-score (ie T-score > -2.5); or a BMD T score of ≤ -2.5 without fragility fractures (Watts et al. Endocr Pract. 2021;27:379-80). Severe (ie established) osteoporosis is a BMD T score of ≤ -2.5 in the presence of one or more fragility fractures.

11.12. The Committee noted the ANZFFR Annual Report 2024 notes that falls and fractures suffered by older people currently lead to under-recognised societal and personal impacts. Examples of these impacts are varied and include family members taking time off paid work to provide care (while acknowledging these can be hard to measure in pure monetary terms), ACC costs of NZ$360 million per year, and contributions to high hospital bed occupancy, which places a significant demand on specialist Health NZ | Te Whatu Ora services and reduces available health care resources.

11.13. The Committee noted the ANZFFR Annual Report 2024 followed 11,600 people with fragility fractures over 2022-2023. The Committee considered this report to be the most comprehensive, up to date evidence reporting on fragility fractures in New Zealand. The Committee noted the demographics for this population were not adjusted for age or ethnicity. The Committee noted that 80% of the population were living at home. The Committee noted that 17% of the population had vertebral fragility fractures, 80% has one of the “big 5” fractures (hip, wrist, spine, pelvis, or upper arm), and 14% had two or more fragility fractures. The Committee noted that only 18% of the 11,600 people were receiving pharmacological treatment for osteoporosis, 96% of whom were taking bisphosphonates.

11.14. The Committee noted that four treatments (all bisphosphonate anti-resorptive agents) are currently funded in New Zealand for the first-line treatment of osteoporosis: alendronate and risedronate (which are oral agents) and the intravenous (IV) infusions pamidronate and zoledronic acid. The Committee noted that in addition to teriparatide, two other treatments are available for the second-line treatment of osteoporosis: raloxifene hydrochloride (oral) – for severe established osteoporosis as an alternative to

bisphosphonates, particularly for those patients with a high risk of invasive breast cancer, and denosumab (subcutaneous (SC) injection) – for severe established osteoporosis after inadequate benefit from a funded anti-resorptive agent.

11.15. The Committee noted 2020 prescribing data showed 16,004 people were newly initiated on bisphosphonate therapy that year. The Committee considered an estimate of ~18,700 people starting on bisphosphonate therapy in 2025 to be appropriate.

11.16. The Committee noted results from the placebo arm of the HORIZON Pivotal Fracture Trial (n=2677 women aged 65 to 85 years old receiving placebo not zoledronic acid), which examined the association between vertebral fracture prevalent at baseline and incident year 1 vertebral fracture (Wustrack et al. Osteoporos Int. 2012;23:53-8). The Committee noted the reported adjusted odds ratios (aOR) were 2.8 for prevalent vertebral fracture (95% confidence interval [CI] 1.9, 4.0) and 3.1 for new year 1 vertebral fracture (95% CI, 1.9, 5.0).

11.17. The Committee noted results from a systematic review that reported the incidence of rate and refracture risk (vertebral and non-vertebral) in people with previous vertebral fragility fractures combining data from 40 randomised controlled trials (RCTs) (Porcu et al. J Endocrinol Invest. 2024;47:795-818). The Committee noted that in untreated people with prior vertebral fragility fractures, the overall rates of subsequent vertebral fragility fractures and non-vertebral fragility fractures were 12 (95% CI 9, 16) and 6 (95% CI 5, 8) per 100 person-years, respectively, equating in effect to respective 12% and 6% average one-year refracture risks.

11.18. The Committee noted a 2004 meta-analysis comprising 15,259 men and 44,902 women reported that previous fracture history was associated with a significantly increased risk of any fracture compared with individuals without a prior fracture (risk ratio [RR] = 1.86; 95% CI = 1.75, 1.98), with similar RRs for osteoporotic fracture or hip fracture (Kanis et al. Bone. 2004;35:375-82).

11.19. The Committee considered that evidence showed people who are very high risk of a fragility fracture are experiencing an unmet health need, due to the morbidity consequences associated with fragility fractures.

*Health benefit*

11.20. The Committee noted teriparatide is a recombinant human parathyroid hormone (PTH) analogue that is injected once daily via subcutaneous (SC) injection (Medsafe datasheet). The Committee noted teriparatide promotes bone formation (ie is anabolic), to treat osteoporosis.

11.21. The Committee noted that many studies outcomes use BMD as a surrogate marker for fracture risk, assessed with DEXA-scan or FRAX score. The Committee considered there is good meta-analysis evidence that BMD is an appropriate surrogate marker for fracture risk, and that there is a clear association between BMD improvement and reduction in fractures (Bouxsein et al. J Bone Miner Res. 2019;34:632-42).

11.22. The Committee noted that teriparatide is recommended, as the first-line treatment for people with very high fracture risk or in those for whom bisphosphonate therapy has been ineffective, by the following bodies:

- American Association of Clinical Endocrinology (Watts et al. Endocr Pract. 2021;27:379-80)
- Osteoporosis Australia Guidelines (The Royal Australian College of General Practitioners. 2017. 2nd edn. South Melbourne, Victoria)
- Endocrine Society (UK)
- International Osteoporosis Foundation

- Asia-Pacific consensus on long-term and sequential therapy for osteoporosis (Tai et al. Osteoporos Sarcopenia. 2024;10:3-10), which it said was based on evidence that anabolic agents increase BMD more rapidly and reduce fracture risk in a shorter time than antiresorptive agents.

*Health benefit as first- versus second- line treatment*

11.23. The Committee noted results from the VERO trial, a randomised, double-blind, placebo controlled trial to compare anti-fracture efficacy of teriparatide with risedronate in post-menopausal women (Kendler et al. Lancet 2018;391:230-40). The Committee noted at 24 months, new vertebral fractures occurred in 5.4% of the teriparatide group and 12.0% of the risedronate group (risk ratio 0.44; 95% CI 0.29, 0.68; *P*<0.0001). The Committee noted that >70% of participants had received previous bisphosphonate therapy, and so considered this study relevant to second-line treatment in much of the population.

11.24. The Committee noted results from a randomised, double-blind, controlled trial, comparing teriparatide with alendronate in people with glucocorticoid-induced osteoporosis (Saag et al. N Engl J Med 2007;357:2028-39). The Committee noted that at the last measurement (18 months), the mean (±SE) bone mineral density at the lumbar spine had increased statistically significantly more in the teriparatide group than in the alendronate group (7.2±0.7% vs. 3.4±0.7%, *P*<0.001); the change from baseline of total hip BMD at 18 months was 3.8±0.6% in the teriparatide group and 2.4±0.6% in the alendronate group, with a significant between group difference of 1.4% (95% CI 0.4, 2.4; *P*=0.005); and significantly fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, *P*=0.004). However, the incidence of nonvertebral fractures was not significantly dissimilar between the two groups (5.6% vs. 3.7%, *P*=0.36).

11.25. The Committee noted results from a prospective, randomised (1:1), open-label, control trial using sequential teriparatide and alendronate compared to alendronate monotherapy in Japanese women (Mori et al. Osteoporos Int. 2023; 34:189-99). The Committee noted the annual incidence rate of morphometric vertebral fracture from 0 to 120 weeks was 0.1020 and 0.1492 in the sequential and monotherapy groups, respectively with a rate ratio of 0.69 (95% CI 0.54 to 0.88, *P* < 0.01). The Committee noted the differences in BMD increases were not significant (*P*=0.09) at 120 weeks.

11.26. The Committee also noted results from the following publications regarding the health benefit of teriparatide as first- versus second- line treatment of osteoporosis:

- Laura et al. Bone Rep. 2021:15:101105
- Wang et al. Medicine (Baltimore). 2017;96:e6970
- Simpson et al. Bone. 2020;130:115081
- Ramchand & Leder. J Clin Endocrinol Metab. 2024;104:303-11
- Boonen et al. J Clin Endocrinol Metab. 2008,93:852-60
- Lyu et al. J Clin Endocrinol Metab. 2019;104:5611-20.

11.27. The Committee considered all the above evidence was reasonably robust to support the possibility that teriparatide is slightly more effective as a first-line agent for treating osteoporosis for people at very high risk of fragility fractures, particularly for reducing the risk of clinical vertebral fractures.

*Health benefit as monotherapy versus combination therapy*

11.28. The Committee noted results from the following publications regarding the use of teriparatide as monotherapy versus as combination therapy with bisphosphonates:

- Cosman et al. J Bone Miner Res. 2011;26:503-1

- Black et al. N Engl J Med. 2003;349:1207-15
- Finkelstein et al. J Clin Endocrinol Metab. 2006;91:2882-7
- Cosman et al. J Clin Endocrinol Metab. 2009;94:3772-80.

11.29. The Committee considered the above evidence indicated that combining teriparatide with bisphosphonates did not result in significant improvements in comparison to teriparatide monotherapy. The Committee considered it to be broadly accepted that there is not good quality evidence to support teriparatide/bisphosphonate combination therapy being superior for treating osteoporosis over teriparatide monotherapy.

*Health benefit – treatment discontinuation*

11.30. The Committee noted expert opinion received by Pharmac that although teriparatide's anti-fracture effect seems to persist for some time (18 months demonstrated in literature), its effect seems to wane off after treatment cessation, if not followed by another anti-osteoporosis medication. The expert opinion considered that this waning may perhaps be faster than that observed with cessation of treatment with potent bisphosphonate therapy (alendronate or zoledronic acid) but not as rapidly as seen with cessation of denosumab treatment.

11.31. The Committee considered the published literature supported this expert opinion, and considered that a proportion of benefit gained from teriparatide is lost after approximately 1 year to 18 months if treatment is not followed by ongoing bisphosphonate therapy (Bone et al. J Clin Endocrinol Metab. 2018;103: 2949–57, Black et al. N Engl J Med. 2005;353: 555-65).

*Suitability*

11.32. The Committee noted teriparatide subcutaneous injections come in prefilled pens that people can self-inject, and subcutaneous needles are required for people to be able to administer their medicine. The Committee noted people being treated with funded teriparatide do not have access to funded subcutaneous needles, as these are currently funded only for insulin or liraglutide administration.

11.33. The Committee noted that the Endocrinology SAC considered, as treating clinicians, that when offered either once yearly zoledronic acid infusion(s) or once daily subcutaneous injections of teriparatide for up to 18 months, people would be more likely to choose yearly infusions of zoledronic acid. The Endocrinology SAC estimated that 10% of people would choose the daily teriparatide injections. PTAC considered this estimation reasonable.

*Cost and savings*

11.34. The Committee noted the cost of teriparatide was higher than the cost of bisphosphonate therapy.

11.35. The Committee considered that, after noting a risk ratio for vertebral fractures (but not other fragility fractures) compared with bisphosphonates of between 0.2 and 0.4 (absolute reduction of around 6%), then approximately 6% of people per year in the high-risk group could avoid spinal fragility fractures by initiating treatment with teriparatide rather than bisphosphonates. The Committee considered this could result in associated savings related to direct healthcare costs and costs to the community and whānau due to spinal fractures.

*Summary for assessment*

11.36. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for teriparatide if it were to be funded in New Zealand for the first line treatment of osteoporosis. This PICO table captures key clinical aspects of the proposal and may be

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

| | |
|---|---|
| **P**opulation | People with very severe established osteoporosis who have not received any previous anti-osteoporosis treatment, AND either have had at least two fractures due to minimal trauma or have had a clinical vertebral fracture, AND have either a BMD T-score ≤ -3.0 (when DEXA is feasible) or 10-year risk of hip fracture ≥ 4.5% or clinical equivalent (as per criterion 2.2 and Note b) of the proposed Special Authority criteria)<br><br>Ie teriparatide as first-line in very high-risk osteoporosis<br>. |
| **I**ntervention | Teriparatide, 20 mcg subcutaneously once-daily for 18 months<br>- Teriparatide to be administered as monotherapy as there is no clear evidence of additional benefit with combination therapy<br>- Teriparatide would be followed by second-line bisphosphonates |
| **C**omparator(s) (NZ context) | First-line bisphosphonates (either alendronate, zoledronic acid, pamidronate or risedronate), followed by teriparatide if the patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a bisphosphonate<br><br>ie teriparatide as second-line, in patients with very high risk osteoporosis. |
| **O**utcome(s) | Improvement in bone mineral density compared to first-line bisphosphonates, measured by DEXA or other means if DEXA is not practicable or available (eg rural populations, very frail elderly with limited mobility).<br>Reduction in fragility fracture incidence<br>Reduction in vertebral fracture incidence<br>Improved health related quality of life<br>Potential mortality benefit (uncertain) |

*Table definitions:*

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

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

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

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