PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 17 November & 18 November 2022

This meeting was held in person

PTAC Pharmacology and Therapeutics Advisory Committee

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1. Present:

PTAC members:
Jane Thomas (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Jennifer Martin (Part of meeting)
Lisa Stamp
Matthew Strother
Rhiannon Braund
Robyn Manuel
Simon Wynn Thomas
Stephen Munn
Tim Stokes
Elizabeth Dennett

Apologies:
Giles Newton Howes

2. Summary of recommendations

2.1. The following recommendation summary is in order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
9.47 Clodronate for osteoradionecrosis.	**Decline**
10.4 pertuzumab-trastuzumab SC for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer in combination with chemotherapy at high risk of recurrence	**deferred**, pending CTAC's assessment
10.5. pertuzumab-trastuzumab SC for the adjuvant treatment of individuals with HER2-positive early breast cancer at high risk of recurrence in combination with chemotherapy	**Deferred**, pending the final overall survival analysis of the APHINITY study
10.6. pertuzumab-trastuzumab SC for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel	**Cost-neutral** to the combined cost of the single IV agents
11.4. liraglutide for the treatment of obesity (individuals with BMI 55kg per m2 and over, with high cardiovascular risk, without T2DM, unable to access bariatric surgery; or Māori or Pacific people with BMI 50kg per m2 and over, with high cardiovascular risk, without T2DM)	**Deferred**
12.4. eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed following two prior lines of chemotherapy	**Declined**
13.4. del-Nido cardioplegia (Biomed)	**High priority**
14.5. physostigmine for the treatment of moderate to severe central and peripheral anticholinergic toxicity	**High priority**

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

3.1. 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.

3.2. 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.

3.3. 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.

3.4. 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.

4. Record of PTAC meeting held 18 August & 19 August 2022

4.1. The Committee reviewed the record of the PTAC meeting held on 18 August & 19 August 2022

4.2. The Committee Accepted the record.

5. Specialist Advisory Committee Record

Immunisation Specialist Advisory Committee May 2022 meeting

5.1. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee meeting held on 9 May 2022. The Committee noted the recommendations made by the Advisory Committee.

5.2. The Committee specifically noted the Advisory Committee's recommendation to fund zoster vaccine (Shingrix) with a high priority for all people from 50 to 64 years of age, and a further recommendation with a low priority for Māori and Pacific people 60 or over. The Committee noted that the Advisory Committee had considered that although Māori and Pacific people have a lower reported incidence of zoster, there is a lower life expectancy and higher prevalence of complications and incidence of hospitalisation from herpes zoster infection in this population. The Committee considered that the low priority recommendation did not reflect the higher health need of Māori and Pacific people from an earlier age than non-Māori, non-Pacific people, and that the recommendation for the sub-group should have at least the same priority as the wider group from 60 to 64 years of age.

5.3. The Committee requested that the Advisory Committee provide further rationale for the low priority recommendation for funding for Māori and Pacific people 60 years of age and over. The Committee also requested that the Advisory Committee consider whether it would like to revise the priority of its recommendation for Māori and Pacific people from 60 years of age.

Respiratory Specialist Advisory Committee April 2022 meeting

5.4. The Committee noted the record of the Respiratory Advisory Committee meeting in April 2022.

5.5. The Committee noted it had seen a draft record relating to the Respiratory Advisory Committee's recommendation and discussion relating to elexacfator/tezacaftor/ivacaftor (Trikafta) for cystic fibrosis as part of PTAC's consideration of the funding application in May 2022.

5.6. The Committee noted the Respiratory Advisory Committee's recommendation and discussion regarding adrenaline auto-injectors for the first aid treatment of anaphylaxis. The Committee noted Pharmac had recently consulted on a proposal to fund adrenaline auto-injectors, subject to eligibility criteria.

5.6.1. The Committee noted the current inequities resulting from the funding of replacement adrenaline auto-injector devices by ACC. This benefited those who were able to afford to self-fund device(s). The Committee considered this access inequity would be substantially reduced if Pharmac was to fund adrenaline auto-injectors.

5.7. The Committee noted the Respiratory Advisory Committee's recommendation and discussion regarding mepolizumab for the treatment of relapsed or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

5.8. The Committee had no further comments regarding the record.

6. Correspondence & Matters Arising

Fluticasone with Vilanterol, 200/25, high dose – Asthma

Application

6.1. The Advisory Committee reviewed correspondence from GlaxoSmithKline (GSK) regarding the funding application for high dose fluticasone with vilanterol (200/25) for the treatment of severe asthma (application received in August 2014).

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

Recommendation

6.3. The Committee did not consider its previous recommendation for high dose fluticasone with vilanterol (200/25) should be updated at this time.

6.3.1. The Committee noted the unmet health need for people with severe asthma, particularly for Māori and Pacific peoples. However, the Committee considered the correspondence from GSK provided no additional evidence since the Committee's last review of the application and therefore considered the previous recommendation remained appropriate.

6.3.2. The Committee acknowledged the medium priority recommendation made in the October 2020 Respiratory Subcommittee meeting. The Committee noted that PTAC and the Specialist Advisory Committees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

Discussion

6.4. The Committee noted that the application for high dose fluticasone with vilanterol (200/25) for the treatment of severe asthma has been considered by PTAC and the Respiratory Subcommittee multiple times:

- Nov 2014 PTAC: Decline
- Sep 2015 Respiratory Subcommittee: Decline
- Nov 2015 PTAC: No formal recommendation
- September 2020: Additional information received from supplier
- Oct 2020 Respiratory Subcommittee: Medium priority
- February 2021 PTAC: Request to review application
- May 2021 PTAC: Decline

6.5. The Committee noted the correspondence from the supplier (GSK) included feedback addressing PTAC's concerns highlighted in the May 2021 PTAC meeting. The Committee noted that this correspondence provided no new evidence regarding the health benefit of high dose fluticasone with vilanterol (200/25) for the treatment of severe asthma.

6.6. The Committee considered that the Respiratory Advisory Committee took a facilitative, clinically pragmatic approach in its review of this funding application at the Oct 2020 Respiratory Subcommittee meeting. The Committee considered that at the May 2021 PTAC meeting it had conducted a more stringent, statistically-based analysis of data, resulting in a decline recommendation. The Committee considered that this

recommendation was based on evidence that high dose fluticasone with vilanterol (200/25) provided little health benefit over and above that of currently funded treatments. It was noted that, in May 2021, the Committee considered this treatment would not address the unmet health need for people with severe asthma and would not address inequities for Māori and Pacific peoples. The Committee noted its previous considerations regarding the availability of funded alternatives and the risk associated with high dose inhaled corticosteroid (pneumonia).

6.7. The Committee clarified its view regarding the impact of this funding application on health inequities in Aotearoa New Zealand. The Committee noted that the Respiratory Advisory Committee had previously commented that funding a combination inhaler such as high dose fluticasone with vilanterol (200/25) would improve adherence in those with severe asthma, whereas PTAC had previously noted evidence that showed this did not impact adherence. The Committee considered that its review of applications has an increased emphasis on equity, and that this may be based on clinical assumptions (particularly where there is not readily available, high-quality evidence). The Committee considered that Māori and Pacific peoples are disproportionately affected by asthma with increased hospitalisation rates, compared with non-Māori, non-Pacific peoples. The Committee considered that Māori also have reduced access to health services and opportunities to improve health literacy and are also more likely to live in areas of greater socioeconomic disadvantage than non-Māori, non-Pacific peoples. The Committee considered that this suggests that the availability of a single, combination inhaler therapy to treat severe asthma may provide potential health benefits to Māori and Pacific peoples. The Committee considered that these equity considerations could assist Pharmac in its decision making.

6.8. The Committee also noted the supplier's suggestion to include specialist review as part of the proposed Special Authority criteria to limit the risk of over-prescribing and target the population with the highest health need. Members considered that introducing specialist funding criteria is likely to reduce accessibility and potentially drive inequities, and that such treatment could be appropriately managed in primary care.

Myeloma NZ correspondence and presentation to PTAC

6.9. The Committee noted correspondence received from Myeloma NZ to Pharmac, which outlined the unmet need for funding of treatments for people with multiple myeloma.

6.10. The Committee viewed a presentation from Myeloma NZ, highlighting the unmet health need in myeloma through the lived experiences of New Zealand patients and their request for the funding of daratumumab.

Discussion

6.11. The Committee noted the specific request from Myeloma NZ for the funding of daratumumab for people with multiple myeloma. The Committee appreciated and valued the patient stories shared by Myeloma NZ and the māia (courage) of the people involved in sharing these.

6.12. The Committee noted that both PTAC and the Cancer Treatments Advisory Committee had already considered the funding application for daratumumab for people with relapsed or refractory multiple myeloma, recommended that it be funded, and that the proposal had been ranked as an option for investment.

6.13. The Committee noted that lenalidomide upfront for both transplant eligible and ineligible patients has been ranked as an option for investment, and that daratumumab, carfilzomib and pomalidomide for people who have received one prior line of therapy has also been ranked as an option for investment.

6.14. The Committee noted an early draft record of the review by CTAC, at its October meeting, of the correspondence from Myeloma NZ to Pharmac. The Committee considered there to be no substantial new evidence that had not previously been considered by either PTAC or CTAC. However, the Committee did note an updated overall survival analysis from the CASTOR trial. The Committee noted the substantial improvement in OS presented for the intention to treat population (hazard ratio (HR) 0.74, 95% CI 0.59-0.92), with the most profound benefit seen in those who have received one prior line of therapy (HR, 0.56 95% CI: 0.39-0.80) (Sonneveld et al. HemaSphere. 2022; 6:12).

6.15. The Committee noted that the POLLUX trial has not been formally reviewed by CTAC. However, members noted the considerations of CTAC in relation to the two meta-analyses (Botta et al. Blood Adv. 2017; 1(7):455-66; van Beurden-Tan et al. J Clin Oncol. 2017; 35(12):1312-1319), and that the efficacy of the combination regimen (lenalidomide and dexamethasone or bortezomib and dexamethasone) would largely depend on an individual's prior exposure to therapy.

6.16. The Committee considered that it would be appropriate to defer to CTAC for their review of the evidence provided in the correspondence. The Committee considered it was confident in the treatment reviews for myeloma by CTAC and that the considerations of CTAC were in line with the considerations of Myeloma NZ.

6.17. The Committee noted that CTAC and the correspondence from Myeloma NZ highlighted that limited access to daratumumab may limit access to global clinical trials, but the Committee considered that this was not something that was unique to this tumour stream, or other disease areas in general.

6.18. The Committee noted a study investigating the trends in myeloma incidence, mortality and survival (Sneyd et al. Cancer Epidemiol. 2019; 60:55-59). The Committee considered that overall the incidence of multiple myeloma is increasing. However, the Committee considered that it is difficult to ascertain if rates for Māori are increasing, disproportionate to non-Māori, due to the small numbers involved. The Committee noted that the study reported that in New Zealand, we have seen an increase in survival probability at various timepoints for people with multiple myeloma since 1990. The Committee considered that this was likely driven by increased access to both treatment and autologous haemopoietic stem cell transplantation (AHSCT). The Committee considered it difficult to ascertain the impact of this on Māori, as they were underrepresented in the cohort of individuals involved in this study. The Committee considered that the younger age at diagnosis, may be influencing the indeterminable differences in survival rates reported in this study.

6.19. The Committee noted another study that investigated the mortality of myeloma by ethnicity (Chan et al. Br J Haematol. 2020; 188:692-700). The Committee noted that the authors had used a Cox proportional-hazards model to determine the interactions between covariates and survival. The Committee noted that for the overall cohort, ethnicity was not a significant factor in overall survival. The Committee noted that this paper does reference the worse outcomes for Māori and Pacific people with multiple myeloma, and that this inference is made based on the reduced access to AHSCT for Māori and Pacific people compared to non-Māori, non-Pacific people.

6.20. The Committee considered that while it is uncertain what the drivers for this reduced access are for Māori and Pacific people, they noted that there is differential access to AHSCT across the country. Furthermore, the Committee considered that increased comorbidities or social and financial barriers in access may drive the reduced rates of AHSCT for Māori and Pacific people.

6.21. The Committee also noted a new study, which reported that Māori and Pacific people have worse overall survival compared to non-Māori, non-Pacific people and reported that receipt of AHSCT was the second greatest determinant of outcomes for people with

multiple myeloma, behind receiving treatment at all (Moore et al. Clin Lymphoma Myeloma Leuk. 2022; 22:e762-e769).

6.22. The Committee considered that given the improved outcomes that have been observed in those who have not received AHSCT, since the funding of bortezomib, it would be likely that the funding of daratumumab and other agents would likely provide a greater benefit for the group of individuals for whom AHSCT is not received compared to those who receive AHSCT. The Committee considered that this was in line with the considerations of CTAC, in relation to both access to daratumumab and first line access to lenalidomide.

6.23. The Committee considered that overall better access to currently funded AHSCT would likely result in significant improvements in outcomes for people with multiple myeloma. The Committee noted that demand for and access to AHSCT is currently at crisis point across NZ, the greatest issue being capacity constraints, but also that the access to treatment varies across the country and may result in people needing to travel long distances to access the standard of care. The Committee noted that there is work being undertaken at Te Aho o Te Kahu to help Te Whatu Ora address this issue.

6.24. The Committee noted the significant work that had been done to establish preferences for various agents in each line of therapy by CTAC. The Committee noted that CTAC had indicated its preference for daratumumab, that it has been recommended for funding and that it is something that Pharmac would like to fund.

6.25. The Committee considered that daratumumab is an efficacious treatment, which provides a potential survival benefit in patients with multiple myeloma. However, the Committee considered that it would not transform multiple myeloma into a non-terminal disease for those who receive it. The Committee noted that subcutaneous daratumumab could circumvent some of the significant infusion capacity issues across New Zealand.

6.26. The Committee noted that we don't have comparable funding systems to other countries and want to ensure that future advocacy groups are aware of these limitations/constraints. The Committee considered that it is not appropriate to compare access to daratumumab in New Zealand compared to Australia, as this differential access is something that is not unique to this indication or treatment. The Committee also considered that the availability of novel treatments in the private setting is not something that is unique to New Zealand.

Certolizumab pegol for rheumatoid arthritis

Application

6.27. The Committee reviewed communication regarding certolizumab pegol as a first-line tumour necrosis factor (TNF) inhibitor for rheumatoid arthritis that was received in response to Pharmac's December 2019 Consultation to Decline a number of funding applications, including certolizumab pegol.

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

Recommendation

6.29. The Committee considered that the Rheumatology Advisory Committee should review the PTAC record regarding certolizumab pegol and provide any comments and/or recommendations.

Discussion

Māori impact

6.30. The Committee did not specifically consider the impact of rheumatoid arthritis (RA) on Māori health outcomes at this time, nor did the consultation response provide specific information about the impact of RA or certolizumab pegol on Māori health outcomes.

Background

6.31. The Committee noted that Pharmac received an application for certolizumab pegol for rheumatoid arthritis (RA) in 2011 and that PTAC considered the application in February 2012. The application included evidence from RAPID-1 and RAPID-2: two randomised, placebo-controlled phase III studies of certolizumab pegol in combination with methotrexate in people with active rheumatoid arthritis who have an incomplete response to methotrexate. The primary endpoint of both studies was ACR20 at 24 weeks. At that time:

6.31.1. PTAC members noted that any consideration of the safety profile of certolizumab was hampered by the short duration of the studies relative to the likely treatment duration in the population group proposed for funding.

6.31.2. PTAC recommended that, since there was only short-term evidence for certolizumab pegol, and little clinical need and limited benefit to be gained from funding a third TNF inhibitor, that the application be declined.

Discussion

6.32. The Committee noted that Pharmac received a consultation response from a clinician who highlighted there was long-term evidence now available for the efficacy of certolizumab pegol in rheumatoid arthritis (RA) from open-label extensions of the RAPID 1 and RAPID 2 trials. The respondent also provided evidence for the potential need and benefit of certolizumab pegol in people with RA who are pregnant, noting that they consider certolizumab offers safety advantages in pregnancy for those living with RA or other relevant chronic inflammatory disorders because it does not cross the placenta.

6.33. The Committee noted the following long-term evidence provided by the respondent for certolizumab pegol in RA:

6.33.1. The Committee noted the RAPID-1 trial two-year results reported that certolizumab pegol and methotrexate provided sustained, two-year inhibition of radiographic progression and sustained improvements in RA clinical signs and symptoms, with no new safety signals observed in patients who completed 2 years of treatment (Keystone et al. Rheumatology (Oxford). 2012;51:1628-38).

6.33.2. The Committee noted that after five years in RAPID-1, slightly more than half of patients were still receiving trial treatment and that those still on treatment had sustained ACR20/50/70 responses, although members considered that people who did not receive reasonable responses would cease treatment (Keystone et al. Ann Rheum Dis. 2014;73:2094-100). The Committee noted that almost all who received certolizumab pegol experienced adverse events (AEs; 93.8%) and that serious AEs (SAEs) were reported in 41.6% although members considered this was expected with tumour necrosis factor inhibitors (TNFi).

6.33.3. The Committee noted that after five years in RAPID-2, about half of patients were still receiving trial treatment and ACR50/70 persistence in those still on treatment was similar to that in RAPID-1 (Smolen et al. Arthritis Res Ther. 2015;17:245). Members noted the trial did not provide data regarding treatment switches.

6.34. The Committee was made aware of the randomised (1:1), single-blind, head-to-head EXXELERATE trial of certolizumab pegol vs adalimumab in 915 patients with RA which was not provided by the respondent (Smolen et al. Lancet. 2016;388:2763-74). The

Committee noted that the primary endpoints were ACR20 at 12 weeks and low disease activity (LDA) at 104 weeks, and that patients who did not receive a response at 12 weeks would switch to the other treatment. The Committee considered that the ACR20/50/70 responses were the same with both treatments and that those who responded to the initial agent had an identical response at two years. The Committee noted that of those who switched (in either direction), about 60% received a good response and that there were no differences in AEs between groups out to two years.

6.35. The Committee was made aware of a meta-analysis of comparative (but mostly indirect) effectiveness of biological medicines in RA by Janke et al. (BMJ. 2020;370:m2288) which reported a difference only in AE profile with certolizumab pegol being associated with a higher rate of SAEs, although members noted that this was not reflected in the head-to-head EXXELERATE trial.

6.36. The Committee considered that it may be reasonable to reconsider certolizumab pegol for treatment of RA, although in the first-line setting it would not be superior to adalimumab and could convey a worse AE profile, although this is uncertain. The Committee considered that the comparator for any economic assessment would be generic adalimumab and therefore there would not likely be any cost saving in this space. The Committee considered it was unclear whether certolizumab pegol would offer benefits as another RA treatment option in a subsequent line, noting there are three funded TNFi for RA, and it was possible that a greater benefit could be gained by considering product with different mechanism of action instead.

6.37. The Committee noted the following evidence provided by the respondent regarding the potential need and benefits of certolizumab in individuals who are pregnant:

6.37.1. The use and safety of TNF inhibitors during pregnancy in women with psoriasis: A review (Johansen et al. Int J Mol Sci. 2018;19:1349)

6.37.2. Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease (Cheent et al. J Crohns Colitis. 2010;4:603-5)

6.38. The Committee was made aware of a study including 188 patients of which about half with RA used a TNFi during pregnancy (Smeele et al. Ann Rheum Dis. 2022;81:1367-73). The Committee noted that TNFi was stopped at the gestational age (GA) as recommended by the European-Alliance-of-Associations-for-Rheumatology; at 20 weeks for adalimumab and infliximab; 28-32 weeks for etanercept, and 38 weeks for certolizumab pegol. Members noted that certolizumab pegol was used right through to 38 weeks as the only risk related to maternal infection at birth and considered that perhaps eight or nine 200 mg doses would be used over the course of pregnancy if certolizumab pegol were to be used from 20 weeks in place of one of the three funded TNFi. The authors reported that TNFi use during pregnancy was associated with increased birth weight of offspring of women with well-controlled RA. Members considered that other outcomes were not different although noted a lower caesarean rate was reported for those not on TNFi.

6.39. The Committee considered that this evidence suggests certolizumab pegol could be considered in pregnancy according to the European guidelines and that the available data suggests it would be safe for mother and baby although benefits over other treatment options were unclear. Members considered that certolizumab has been assessed in the literature for the treatment of other conditions (eg psoriasis) during pregnancy but was not thought to add a lot of benefit.

6.40. Members considered that with three funded TNFi available there is not currently an unmet need in terms of RA management during pregnancy, due to either the occurrence of disease remission, a preference to not take a TNFi over that time, or the presence of active disease requiring treatment. Members also considered that it was common to

extend the dosing interval of anti-TNFs during pregnancy and discontinue treatment after approximately 24 weeks. Members considered that in pregnancy, the management of an individual's RA would be guided by their rheumatologist, while those who are pregnant and living with highly complex RA (eg those with limited hip movement or other complexities) would also be cared for by an obstetrician. Members considered that the key risk of RA treatment with certolizumab pegol during pregnancy was a six-month risk of infection for the baby, which would impact the infant's ability to receive any live vaccines until at least five months after last dose during pregnancy. Members further considered that funding certolizumab pegol as an additional treatment option for RA in pregnancy could add unnecessary complexity during pregnancy from treatment switching.

General

6.41. The Committee considered that it was unclear whether there was a need for certolizumab for the treatment of RA and where this might fit into the treatment paradigm. The Committee therefore considered that the Rheumatology Advisory Committee should review the PTAC record regarding certolizumab pegol and provide comments and/or recommendations.

Clodronate - Osteoradionecrosis

Application

6.42. The Committee reviewed the feedback relating to the consultation to decline the application for clodronate for osteoradionecrosis.

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

Recommendation

6.44. The Committee **recommended** that the application for clodronate for the treatment of osteoradionecrosis be **declined**.

Discussion

Background

6.45. The Committee noted that a clinician application for clodronate for the treatment of osteoradionecrosis was recommended for decline by PTAC in February 2011. At the time, the Committee considered that the evidence supporting the use of clodronate as a treatment for osteoradionecrosis was weak with only two non-experimental cohort studies available, and that there was no evidence of health benefit from clodronate provided by the applicant or in any other literature it reviewed.

6.46. The Committee noted that in 2019, Pharmac publicly consulted on declining a number of funding applications, including clodronate for osteoradionecrosis. The Committee noted that one reply was received regarding the use and efficacy of PENtoxifylline+TOcopherol+CLOdronate (ie PENTOCLO protocol) in treatment of osteoradionecrosis. The Committee noted that pentoxifylline and tocopherol are already available without restriction, and that the PENTO protocol utilising these drugs is also used in the treatment of osteoradionecrosis.

Discussion

6.47. The Committee noted that osteoradionecrosis occurs when irradiated bone becomes devitalised and exposed through the overlaying skin or mucosa without healing for three months or more, and that this typically occurs in the mandible. The Committee noted that

the majority of cases occur within the first three years of radiotherapy, and that radiotherapy in combination with chemotherapy may increase the risk of developing osteoradionecrosis even further. The Committee noted that other risk factors include poor oral hygiene, and tobacco and alcohol use.

6.48. The Committee noted that conservative management of osteoradionecrosis can involve antibiotic treatment, improvement in oral hygiene, and medical management with pentoxifylline and tocopherol. The Committee noted that hyperbaric oxygen treatment has also occasionally been used in the treatment of osteoradionecrosis and considered that this treatment is ineffective. The Committee also noted that surgical treatment is an option for individuals who have more severe osteoradionecrosis, or for whom conservative management was ineffective or inappropriate.

6.49. The Committee noted that pentoxifylline is suggested to improve blood flow and vascularisation, tocopherol is an anti-oxidant vitamin-E analogue, and that clodronate is a bisphosphate added to promote osteoblast differentiation and osteogenesis (Breik et al. Int J Oral Maxillofac Surg. 2019;48:1022-7).

6.50. The Committee noted the following evidence relating to the use of clodronate in the PENTOCLO regimen for the treatment of osteoradionecrosis:

6.50.1. Kolokythas et al. Int J Oral Maxillofac Surg. 2019;48:173-80: a meta-analysis including seven studies on the use of pentoxifylline and tocopherol with or without clodronate for the treatment of osteoradionecrosis which reported that the current literature supports the use of clodronate in this setting.

6.50.2. Delanian et al. Head Neck. 2005;27:114-23: a cohort study in which 18 patients were treated with the PENTO combination, with the eight most severe patients being treated with PENTOCLO. The Committee noted that all patients improved but considered it unclear if clodronate provided any additional benefit over the PENTO combination regimen.

6.50.3. Patel et al. Radiother Oncol. 2021;156:209-16: a retrospective study of patients with osteoradionecrosis treated with either PENTO or PENTOCLO which reported that 54.4% of patients had healed after 12.9 months, and that PENTO was significantly superior to PENTOCLO.

6.50.4. Dissard et al. Laryngoscope. 2020;130:E559-66: a prospective cohort study of patients with mandibular osteoradionecrosis treated with PENTOCLO which reported that exposed bone area decreased by 92% at 24 months.

6.51. The Committee considered that the above evidence was of low strength and quality.

6.52. Committee noted that while there have been no randomised controlled trials of clodronate for osteoradionecrosis to date, the RAPTOR trial (an unblinded, randomised, controlled trial) which aims to compare standard supportive care (SSC) against SSC plus PENTOCLO, measuring time-to-healing as primary endpoint, is currently being conducted. The Committee therefore considered that a funding recommendation for clodronate in this indication should be declined pending further review subsequent to a funding application following publication of trial results for the RAPTOR trial, which are expected in 2026, and/or if any other relevant evidence becomes available.

7. Pertuzumab and trastuzumab (subcutaneous) - Additional option in individuals eligible for funded IV pertuzumab and trastuzumab

Application

7.1. The Committee reviewed the application from Roche Products NZ Ltd for the use of PHESGO pertuzumab and trastuzumab, a combined product containing two treatments that is administered subcutaneously (SC). The Committee noted that the application proposes that this formulation ("pertuzumab-trastuzumab SC") is funded in the community and in hospital as an additional option for people eligible for funded intravenous (IV) pertuzumab and trastuzumab for the following indications:

7.1.1. Neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either >2 cm or node positive) in combination with chemotherapy as part of a complete treatment regimen for early breast cancer

7.1.2. Adjuvant treatment of individuals with HER2-positive early breast cancer at high risk of recurrence in combination with chemotherapy

7.1.3. HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel for those who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease

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

Recommendation

7.3. The Committee **recommended** that pertuzumab-trastuzumab SC for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer in combination with chemotherapy at high risk of recurrence be **deferred,** pending CTAC's assessment of the additional data provided for pertuzumab in the neoadjuvant setting.

7.4. The Committee **recommended** that pertuzumab-trastuzumab SC for the adjuvant treatment of individuals with HER2-positive early breast cancer at high risk of recurrence in combination with chemotherapy be **deferred,** pending the final overall survival analysis of the APHINITY study planned to be conducted in approximately 2024.

7.5. The Committee **recommended** that pertuzumab-trastuzumab SC for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel be funded **only if cost-neutral** to the combined cost of the single IV agents.

Initial application — metastatic breast cancer
Applications only from any relevant practitioner. Approvals valid for 12 months.
All of the following:
1. The person has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
2. Either:
    2.1. Their disease is chemotherapy treatment naïve; or
    2.2. Patient has not received prior treatment for their metastatic disease and has had a treatment free interval of at least 12 months between prior (neo)adjuvant chemotherapy treatment and diagnosis of metastatic breast cancer; and
2. The individual has good performance status (ECOG grade 0-1); and
3. Pertuzumab-trastuzumab SC to be discontinued at disease progression.

Renewal — metastatic breast cancer
Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
1. The cancer has not progressed at any time point during the previous 12 months whilst on pertuzumab-trastuzumab SC.

7.5.1. In making this recommendation, the Committee considered the evidence of non-inferiority between the SC formulation and the current IV standard of care treatment regimen which is relevant to the treatment of this population with metastatic breast

cancer in New Zealand, and the fiscal implications of the competition for supply of IV trastuzumab and upcoming patent expiry of pertuzumab.

Discussion

Māori impact

7.6. The Committee considered that the high health need of people with breast cancer in New Zealand including the high impact on Māori has been previously considered by CTAC and PTAC. Members considered that the incidence of HER-2 positive breast cancer was likely proportional between Māori and non-Māori.

Background

7.7. The Committee noted that intravenous (IV) pertuzumab is funded for the treatment of metastatic breast cancer (mBC) and IV trastuzumab is funded for both early breast cancer (eBC) and mBC, subject to funding criteria.

7.8. The Committee noted that a funding application for subcutaneous trastuzumab (Herceptin) was initially recommended for decline by PTAC in November 2014 then received a low priority recommendation from the Cancer Treatments Subcommittee (CaTSoP; now the Cancer Treatments Advisory Committee) in March 2015. In November 2015. In November 2015, PTAC recommended it be funded only if cost neutral to the IV formulation of trastuzumab (with cost neutrality taking into account future entry of IV trastuzumab biosimilars and associated price decreases).

7.9. The Committee noted that a funding application for the use of pertuzumab and trastuzumab as neoadjuvant therapy in early breast cancer was recommended for decline by CaTSoP in September 2018 due to insufficient evidence available at that time. The Committee noted that Pharmac received correspondence and additional data for the neoadjuvant indication from the supplier in 2021 and this information was considered by CTAC in October 2022, Pharmac is currently reviewing the applications consultation feedback.

Health Need

7.10. The Committee considered that the high health need of people with breast cancer in New Zealand, including the high impact on Māori, has been previously considered by CTAC and PTAC. Members considered that the incidence of HER-2 positive breast cancer was likely proportional between Māori and non-Māori.

7.11. The Committee noted that the treatment paradigms provided in the supplier's application reflected current practice, although noted that the proposed use of pertuzumab in eBC would introduce an additional medicine for neoadjuvant and adjuvant treatment regimens. The Committee considered that current treatments could be summarised as follows:

7.11.1. Neoadjuvant (before surgery): IV trastuzumab with chemotherapy (subsequently, these individuals may be eligible to receive trastuzumab emtansine as an adjuvant treatment)

7.11.2. Adjuvant (after surgery): IV trastuzumab with chemotherapy, or trastuzumab emtansine (subsequently, these individuals may complete the remainder of 12-month trastuzumab regimen)

7.11.3. Metastatic: IV trastuzumab and chemotherapy, as monotherapy or in combination with IV pertuzumab (subsequently, may be eligible to receive trastuzumab emtansine if the individual has not received prior funded trastuzumab emtansine in the adjuvant setting).

Health Benefits

7.12. The Committee noted that the subcutaneous combination product, pertuzumab-trastuzumab SC, contains pertuzumab and trastuzumab which are currently listed in the Pharmaceutical Schedule and are both rhIG monoclonal antibodies that target the HER2 receptor to mediate antibody-dependent cell-mediated cytotoxicity. The Committee noted that it also contains vorhyaluronidase alfa, a glycosylated single-chain protein produced by Chinese Hamster Ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase that is used to increase absorption when given by subcutaneous injection.

7.13. The Committee noted that the requested indications are Medsafe approved. The Committee noted that pertuzumab-trastuzumab SC is administered as a subcutaneous injection given as a loading dose (1200 mg pertuzumab / 600 mg trastuzumab) followed by maintenance doses every 3 weeks (600 mg pertuzumab / 600 mg trastuzumab). The Committee considered that treatment administration as proposed in the application was reasonable and supported by the literature in each setting, and could be summarised as follows:

7.13.1. Neoadjuvant: pertuzumab-trastuzumab SC for three to six cycles depending on the regimen chosen in combination with chemotherapy. Individuals who start pertuzumab-trastuzumab SC in the neoadjuvant setting should continue to receive adjuvant treatment to complete 1 year of treatment (maximum 18 cycles).

7.13.2. Adjuvant: administered for a total of one year (maximum 18 cycles or until disease recurrence, or treatment-limiting toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard chemotherapy. Pertuzumab-trastuzumab SC treatment should start on day one of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

7.13.3. Metastatic: pertuzumab-trastuzumab SC should be administered in combination with docetaxel until disease progression or unmanageable toxicity. Treatment with pertuzumab-trastuzumab SC may continue even if docetaxel is discontinued.

7.14. The Committee considered that its appraisal of the potential benefits and risks of pertuzumab-trastuzumab SC should focus on the addition of pertuzumab in eBC, as it is not funded in those indications, and on the IV-SC relationship in mBC given both pertuzumab and trastuzumab IV formulations are funded for use in the metastatic setting. The Committee noted that the evidence in the application pertained to early breast cancer, that evidence for the neoadjuvant setting was submitted with another application being appraised separately, and that no specific evidence was provided in the application for the metastatic setting.

7.15. The Committee noted that FeDeriCa was a phase 3, multicentre, randomised (1:1), open-label, non-inferiority study of 500 adult patients with HER2-positive, operable, locally advanced, or inflammatory stage II–IIIC breast cancer, ECOG performance status (PS) of 0-1, and a left ventricular ejection fraction (LVEF) of ≥55% (Tan et al. Lancet Oncol. 2021;22:85-97; Supplementary Appendix; Correction; Comment by Bartsch et al. 2021). The Committee noted that participants received either IV pertuzumab (840 mg loading dose, then 420 mg maintenance doses) and IV trastuzumab (8 mg/kg loading dose, then 6 mg/kg maintenance doses) or a fixed-dose combination of pertuzumab and trastuzumab for SC injection (1200 mg pertuzumab with 600 mg trastuzumab loading dose in 15 mL, then 600 mg pertuzumab with 600 mg trastuzumab maintenance doses in 10 mL), administered every three weeks with neoadjuvant chemotherapy for both groups.

7.15.1. The Committee noted that the primary endpoint of FeDeriCa was non-inferiority of the Cycle 7 (pre-dose Cycle 8) pertuzumab serum trough concentration (Ctrough) with pertuzumab-trastuzumab SC versus pertuzumab and trastuzumab IV (non-inferiority concluded if the lower bound of the 90% CI of the geometric mean ratio was ≥0.8). The per-protocol pharmacokinetic population comprised 203 patients in the IV group and

206 patients in the fixed-dose combination group. The geometric mean ratio of pertuzumab serum Ctrough SC to serum Ctrough IV was 1.22 (90% CI 1.14–1.31).

7.15.2. The Committee considered that there was a possibility of underdosing the SC treatment in FeDeriCa depending on patient weight. The Committee noted that the cycle 7 endpoint aligned with FDA regulations but considered that it is a statistical rather than clinical endpoint, possibly used to mitigate differences in clearance due to tumour load. The Committee considered that there is an evidence base for efficacy of the IV combination in the metastatic setting and would expect non-inferiority of IV and SC in the metastatic context based on this evidence.

7.16. The Committee noted that PHranceSCa was a phase 2, multicentre, multinational, randomised (1:1), double-blind, open-label, crossover study of 160 adult patients with HER2-positive, inflammatory, locally advanced or eBC who had completed neoadjuvant pertuzumab and trastuzumab with chemotherapy and had subsequently undergone surgery, had ECOG PS of 0-1 and LVEF ≥55% (O'Shaughnessy et al. Eur J Cancer. 2021;152:223-32). The Committee noted that participants received three cycles of either IV pertuzumab and trastuzumab or a fixed-dose SC combination of pertuzumab and trastuzumab at same doses as in the FeDeriCa study, then crossed over to the alternative treatment for another three treatment cycles, then patients chose their preferred route of administration to continue to 18 cycles.

7.16.1. The Committee noted that the primary outcome of PHranceSCa was patient preference for pertuzumab-trastuzumab SC in the modified intention-to-treat (ITT) population. The Committee noted that 136/160 patients (85.0%, 95% CI: 78.5–90.2) preferred pertuzumab-trastuzumab SC whereas 22/160 preferred pertuzumab and trastuzumab IV (13.8%).

7.17. The Committee noted that APHINITY was a phase 3, multinational, multicentre, randomised 1:1), double-blind, placebo-controlled trial of 4,805 patients with nonmetastatic, adequately excised, histologically confirmed invasive HER2-positive breast cancer (Von Minckwitz et al. N Engl J Med. 2017;377:122-31). The Committee noted that participants had either node-positive disease or node-negative disease with a tumour diameter greater than 1.0 cm (node-negative excluded following protocol amendment) and LVEF ≥55%.

7.17.1. The Committee noted that APHINITY participants received either IV pertuzumab (840 mg loading dose, then 420 mg maintenance doses) and IV trastuzumab (8 mg/kg loading dose, then 6 mg/kg maintenance doses) or received IV placebo (840 mg loading dose, then 420 mg maintenance doses) and IV trastuzumab (8 mg/kg loading dose, then 6 mg/kg maintenance doses), administered every three weeks in both groups beginning with the first cycle of taxane therapy. The Committee noted that a maximum interval of eight weeks was required between definitive breast surgery and the first chemotherapy dose. Participants received a total of 18 cycles pertuzumab/placebo and trastuzumab within one year and follow-up was planned to a total of 10 years.

7.17.2. The Committee noted that the primary outcome of APHINITY was invasive-disease–free survival (IDFS), defined as the time from randomisation until the date of first occurrence of either: recurrence of ipsilateral invasive breast tumour; recurrence of ipsilateral locoregional invasive disease; a distant disease recurrence; contralateral invasive breast cancer; or death from any cause. The Committee noted that IDFS in the ITT population was 92.3% with pertuzumab vs 90.6% with placebo at 48 months (stratified hazard ratio [HR] 0.81, 95% CI: 0.66 to 1.00; P=0.045). The Committee noted that IDFS in node positive participants was 89.9% vs 86.7%, respectively (unstratified HR 0.77; 95% CI: 0.62 to 0.96) and in node negative was 96.7% vs 96.2%, respectively (unstratified HR 1.13; 95% CI: 0.68 to 1.86). The Committee considered that IDFS was a large composite endpoint including several measures of

disease recurrence and included treatment-related death, however, the Committee noted that the upper bound of the 95% CI in the ITT population reached one and the unstratified HR for node negative crossed one.

7.17.3. The Committee noted that overall survival (OS) was a secondary outcome of APHINITY and that at the first interim OS analysis, no significant treatment effect with regard to mortality was reported (HR 0.89; 95% CI, 0.66 to 1.21; P=0.47). The Committee noted APHINITY 6 year follow-up data reporting the second interim analysis of OS (Piccart et al. J Clin Oncol. 2021;39:1448-57) and 8 year follow-up data reporting the third interim analysis of OS [Loibl et al. Presented at European Society of Medical Oncology (ESMO) conference, July 2022 (Abstract Nr. VP6-2022]; statistical significance was not reached in either analysis. The Committee noted that the final event-driven OS analysis of APHINITY is planned to be conducted when 640 deaths have occurred, in approximately 2024.

7.18. The Committee noted the following evidence regarding pertuzumab and trastuzumab fixed dose combination or subcutaneous formulations identified by Pharmac staff:

7.18.1. *Analyses of the FeDeriCa study:* Population pharmacokinetic and exploratory exposure-response analysis of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer in the FeDeriCa study (Wang et al. Cancer Chemother Pharmacol. 2021;88:499-512 and correction by Wang et al. 2022).

7.18.2. *Study in healthy volunteers:* Development of a subcutaneous fixed-dose combination of pertuzumab and trastuzumab: Results from the phase Ib dose-finding study (Kirschbrown et al. J Clin Pharmacol. 2019;59:702-16).

7.19. The Committee considered that the evidence in the supplier application came from good quality open-label clinical trials, noting that APHINITY was a large phase III trial with potentially premature interim analyses of OS. The Committee considered that the evidence from APHINITY and evidence of non-inferiority between SC and IV in FeDeriCa were most relevant but lacked rigor in their trial designs. The Committee considered there was some uncertainty in whether there would be non-inferiority in a clinical context, although noted the non-inferiority reported according to the FeDeriCa definitions and endpoints. The Committee considered the evidence to be broadly relevant to the New Zealand population with eBC, although the trials did not include New Zealand participants.

7.20. On balance, the Committee considered that it was reasonable to assume non-inferiority of IV and SC for metastatic disease, however, considered that the benefit from pertuzumab-trastuzumab SC over standard of care treatment with IV trastuzumab and chemotherapy for neoadjuvant and adjuvant treatment of eBC was unclear from the evidence provided. The Committee therefore considered that it should defer the application for adjuvant treatment until publication of the APHINITY final OS analysis in 2024 and should defer its consideration of the neoadjuvant indication pending CTAC's assessment of the additional data provided for pertuzumab in the neoadjuvant setting.

Suitability

7.21. The Committee considered that any time savings from SC treatment duration compared with that of IV administration would be small and not likely meaningful in the context of current healthcare constraints (ie unlikely to free up resources such as beds and staff time by switching from IV to SC). The Committee noted that some treatments that could feasibly be given in primary care are currently given in secondary care to address delivery needs where there is no package of care available for implementation nor capitated funding. The Committee considered that there would be a resource impact even if SC treatment were able to be given in the community, likely conveying an opportunity cost on

general practice. The Committee noted that it was not a safety issue preventing primary care administration of infusions, rather increased capacity would be required as the same infusion services would deliver either SC or IV treatment.

7.22. The Committee considered that there was the potential for a proactive community treatment plan in future in collaboration with Te Whatu Ora, linking to the overall health strategy and including provincial centres for access to a range of treatments (eg inflammatory diseases). Members considered that such a transition to primary care (not necessarily general practice) would offer benefits by enabling access for those living in remote or rural areas, although acknowledged these may not be quantifiable time savings for Pharmac cost-effectiveness assessment.

Costs and Savings

7.23. The Committee considered that funding pertuzumab-trastuzumab SC for mBC, even if cost-neutral, may incur a cost to the healthcare system and a cost to individuals in the community for treatment administration. The Committee noted the competition for supply of IV trastuzumab (with a competitive process currently underway), and therefore considered it was reasonable, at this point in time, to require cost neutrality to the originator pertuzumab and generic trastuzumab. The Committee considered competition for pertuzumab would also be anticipated following patent expiry for this agent, although the Committee noted there were still active patents in New Zealand for the innovator IV pertuzumab. The Committee noted that this proposal would be the originator combination product.

Summary for Assessment

7.24. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab-trastuzumab SC at this time, for neoadjuvant treatment of HER-2 positive early breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear/uncertain at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with HER-2 +ve, locally advanced, inflammatory, or early-stage breast cancer who have not received prior chemotherapy
Intervention	Neoadjuvant subcutaneous injection given as a loading dose (1200 mg pertuzumab / 600 mg trastuzumab) followed by maintenance doses every 3 weeks (600 mg pertuzumab/ 600 mg trastuzumab) in combination with taxane- or anthracycline-based chemotherapy for 3 to 6 cycles depending on the chemotherapy regimen used.
Comparator(s) (NZ context)	Neoadjuvant IV trastuzumab given as a loading dose (8 mg/kg trastuzumab) followed by maintenance doses every 3 weeks (6 mg/kg) in combination with taxane- or anthracycline-based chemotherapy for 3 to 6 cycles depending on the chemotherapy regimen used.
Outcome(s)	To be confirmed following CTAC's assessment of the additional data provided for pertuzumab in the neoadjuvant setting.

Table definitions:

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

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

Comparator: 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).

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

7.25. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab-trastuzumab SC if it were to be funded in New Zealand for adjuvant treatment of individuals with HER-2 positive early breast cancer at high risk of recurrence. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear/uncertain at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with HER-2 +ve, locally advanced, inflammatory, or early-stage breast cancer who have undergone chemotherapy and surgery
Intervention	Adjuvant (after surgery) subcutaneous injection given as a loading dose (1200 mg pertuzumab/ 600 mg trastuzumab) followed by maintenance doses every 3 weeks (600 mg pertuzumab/ 600 mg trastuzumab) in combination with taxane- or anthracycline-based chemotherapy for a maximum of one year. Treatment should continue even if chemotherapy is discontinued.
Comparator(s) (NZ context)	• Adjuvant IV trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance dose) plus chemotherapy administered every 3 weeks for one year or until disease progression • Adjuvant IV trastuzumab emtansine 3.6 mg/kg administered every 3 weeks for a total of 14 cycles or disease recurrence.
Outcome(s)	To be confirmed following APHINITY trial data update in approx. 2024.

Table definitions:

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

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

Comparator: 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).

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

7.26. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab-trastuzumab SC at this time, for treatment of HER-2 positive metastatic or

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

Population	People with HER-2 +ve metastatic or locally recurrent unresectable breast cancer
Intervention	Trastuzumab and pertuzumab subcutaneous injection or IV given as a loading dose (1200 mg pertuzumab/ 600 mg trastuzumab) followed by SC maintenance doses every 3 weeks (600 mg pertuzumab/ 600 mg trastuzumab) in combination with taxane- or anthracycline-based chemotherapy until disease progression
Comparator(s) (NZ context)	IV trastuzumab and pertuzumab given as a loading dose (840 mg pertuzumab/ 8 mg/kg trastuzumab)) followed by maintenance doses every 3 weeks (420 mg pertuzumab/ 6 mg/kg trastuzumab) in combination with taxane- or anthracycline-based chemotherapy for 3 to 6 cycles depending on the chemotherapy regimen used.
Outcome(s)	• No incremental health benefit compared to IV formulation • Potential savings to the health sector due to slightly shorter administration time for the SC formulation
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

8. Liraglutide for the treatment of obesity (people with body mass index 55 kg/m^2 and over, with high cardiovascular risk, without type 2 diabetes mellitus, unable to access bariatric surgery; or Māori or Pacific people with body mass index 50 kg/ m^2 and over, with high cardiovascular risk, without type 2 diabetes mellitus

Application

8.1. The Committee reviewed the application for Liraglutide for the treatment of obesity (in people with BMI 55 kg/m^2 and over, with high cardiovascular risk, without type 2 diabetes mellitus (T2DM), who are unable to access bariatric surgery; or in Māori or Pacific people with BMI 50 kg/m^2 and over, with high cardiovascular risk, without type 2 diabetes mellitus (T2DM)

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

Recommendation

8.3. The Committee **deferred its recommendation** for liraglutide for the treatment of obesity (individuals with BMI 55 kg/m^2 and over, with high cardiovascular risk, without T2DM, unable to access bariatric surgery; or Māori or Pacific people with BMI 50 kg/m^2 and over, with high cardiovascular risk, without T2DM), pending engagement with Te Whatu Ora and the development of Special Authority criteria that better reflect the unmet health need, and requesting further real world evidence in the New Zealand context supporting the use of GLP-1 agonists as a class, for weight loss without significant concurrent lifestyle intervention.

8.4. In deferring their recommendation, the Committee considered the following:

- Health need of people with obesity was high particularly for Māori and Pacific peoples, people of Indian and other South Asian ethnicity, those living with disability or in areas of lower socioeconomic status, and urban areas.

- Efficacy of liraglutide without concurrent significant diet and exercise intervention was not clear, noting that the provision of these interventions across New Zealand is variable. Evidence of real-world efficacy without diet and exercise intervention would strengthen the relevance in the context of the New Zealand population.

- Those proposed for funding (BMI ≥50 or ≥55 kg/m^2) would remain severely obese even after a 5-10% reduction in weight and would remain at risk of cardiometabolic and physical complications related to obesity.

- Inequitable access to bariatric surgery due to high demand compared to low public funding and variable eligibility criteria throughout the country.

- Possibility of bridging therapy for those otherwise eligible for bariatric surgery but their BMI or weight is too high.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding liraglutide for the treatment of obesity (for people with a BMI ≥50 kg/m^2, high cardiovascular risk and without diabetes) on Māori health areas of focus and Māori health outcomes. The Committee considered Māori were inequitably burdened by cardiovascular disease, type 2 diabetes and the need for osteoarthritis associated large joint replacements, conditions for which obesity is a risk factor. The Committee considered that Māori are also more likely than non-Māori to live in areas of higher socioeconomic deprivation, increasing these inequities and potentially increasing inequities of access to treatment.

8.6. The Committee considered that the proposal to fund liraglutide specifically for Māori (and Pacific people with BMI 50 kg/m^2 and over, with high cardiovascular risk, without type 2 diabetes) was not supported by evidence, due to the lack of inclusion of Māori in the SCALE Prediabetes and Obesity trial. The Committee noted that the absence of Māori in the SCALE trial was not atypical for a global trial and considered there to likely be similar benefit for Māori. The Committee also considered that the use of a higher BMI alone to assess cardiometabolic risk, has been based on the body composition of people of European ethnicity and risk profiles and has not been validated in other population groups and therefore may not be generalisable across the latter. The Committee considered the use of waist circumference to be a potential alternative for BMI. The Committee noted there was a significant reduction in waist circumference in the SCALE Prediabetes and Obesity trial in both the 160 week and the 56 week follow up and considered that Māori would likely benefit from this reduction despite the trial not being inclusive of Māori. The Committee considered the significance of 5% weight loss in Māori to be unknown based on the information presented but was likely to be beneficial.

Background

8.7. The Committee noted that obesity is an international issue, and the prevalence of obesity is increasing worldwide. The Committee noted that the current rising cost of living and obesogenic environment, including the advertising of poor nutritional foods, makes weight management extremely difficult.

8.8. The Committee noted that the proposed funding specifically excludes those with diabetes as dulaglutide is currently funded as the sole supply GLP-1 agonist for the treatment of diabetes.

8.9. The Committee noted the proposed groups for funding are as follows:

- Those with a BMI ≥55 kg/m^2, unable to access funded bariatric surgery, with high cardiovascular risk and without diabetes; or

- Māori and Pacific peoples with a BMI ≥50 kg/m^2, with high cardiovascular risk and without diabetes.

Health need

8.10. The Committee considered that the health need was severe and there was an unmet health need for people with obesity (BMI ≥30 kg/m^2). The Committee considered that obesity itself was a risk factor for cardiovascular disease, type 2 diabetes, osteoarthritis and cancer. The Committee noted that the medicalisation of obesity and treatment as a medical condition was not a suitable solution to the unmet health need. The Committee considered that obesity is a public health issue and would require policy and health system changes to make meaningful change. The Committee considered that those who are overweight and at risk of becoming obese would also be positively impacted by system and policy changes. The Committee considered that funding a drug in isolation of other changes was not an appropriate response to the obesity issue but could be considered as part of system changes. The Committee considered the access to weight management services such as psychological support services, Green Prescription, and diet counselling services and publicly funded bariatric surgery is highly variable across the country and many obese people will not have any access to these services. The Committee noted the significant proportion of New Zealand's population considered to be obese (based on BMI) reflected the high unmet health need.

8.11. The Committee considered the health need of the person's family/whānau to be severe due to the transgenerational effect of obesity. The Committee considered the influence of behaviour observed in the home or family environment to be significant. The Committee considered that the effect of discrimination against those who are over-weight within society limited people's ability to get paid employment with potential impacts to their family.

8.12. The Committee considered many groups had inequities in obesity including Māori, Pacific peoples, Indian and other South Asian ethnicities, people living with disability, those living in areas of low socioeconomic status and those residing in urban areas. The Committee considered Māori were also inequitably burdened by cardiovascular disease, type 2 diabetes and osteoarthritis-associated large joint replacement, conditions for which obesity is a risk factor. The Committee also considered that Pacific women, in particular are burdened by class III obesity (BMI >40 kg/m^2) more than any other ethnicity and gender. The Committee considered those facing inequities to have additional burden of obesity resulting in a higher unmet health need in these groups. The Committee considered that an inequitable access to effective management or a treatment plan for obesity also resulted in a higher unmet health need in these groups.

Health benefit

8.13. The Committee noted the evidence presented in the application was funded by the supplier and considered the strength and quality to be high. The Committee noted that there was no New Zealand recruitment to any of the studies presented. The Committee noted the below key evidence:

- Pi-Sunyer X et al. N Engl J Med. 2015;373:11-22 (SCALE Obesity and Prediabetes trial)
  A phase III, randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational trial in participants with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) (n = 3,731). Participants were assigned in a 2:1 ratio to receive liraglutide 3.0 mg or placebo as an adjunct to diet and exercise interventions. Participants were stratified according to prediabetes status (normoglycemic and prediabetic) and BMI (≥30 kg/m^2 vs <30 kg/m^2). The trial was continued for up to 56 weeks for normoglycemic participants and 160 weeks follow-up for prediabetic participants, both with 12 weeks off-drug follow up. The primary outcomes were ≥5% weight loss (63.2% v 27.1%), ≥10% weight loss (33.1% v 27.1%) and mean weight loss (8.4 v 2.8 kg, mean difference of – 5.6 kg). The secondary outcomes were reduction in waist circumference, systolic and diastolic blood pressure, HDL, LDL and VLDL and improvements in prediabetic markers (HbA1c, fasting glucose and insulin) as well as HRQoL. Investigators noted that the clinical relevance of these improvements is uncertain. The safety profile of liraglutide was consistent with findings in previous reports. The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhoea. Serious events occurred in 6.2% of the participants in the liraglutide group and in 5.0% of the participants in the placebo group.

- le Roux CW et al. Lancet. 2017; 389:1399-1409
  Continuing on from the initial 56-week follow-up in the SCALE Obesity and Prediabetes trial (above), a 160-week treatment with liraglutide and diet and exercise compared to only diet and exercise with 12 weeks off-drug follow up for prediabetic participants only. The primary outcomes were diagnosis of diabetes (2% v 6%), mean weight loss (–6·1% v –1·9%), ≥5% weight loss (49.6% v 23.7%), >10% weight loss (24.8% v 9.9%) and >15% weight loss (11.0% v 3.1%). The secondary outcomes were waist circumference, systolic blood pressure and regression of prediabetes to normoglycemia. The safety profile of liraglutide up to week 160 was similar to the previous findings in the follow up to week 56. After treatment cessation at week 160, some weight was regained in the liraglutide group, although the treatment difference was still significant at week 172 (–3·2%, 95% CI –4·3 to –2·2, P<0·0001).

- Fujioka K et al. Obesity (Silver Spring). 2016;24:2278-88
  Early responders without type 2 diabetes, were found to be more likely to achieve weight loss at week 56. Using pooled data from the SCALE Obesity and Prediabetes and SCALE Diabetes trials, weight loss of ≥4% at 16 weeks best predicted ≥5% weight loss after 56 weeks. Weight loss and changes in cardiometabolic risk factors (HbA1c, blood pressure, HDL, and LDL) and health-related quality of life were evaluated on completing 56 weeks' treatment in those without type 2 diabetes. The early response criterion was clinically useful to identify individuals who would achieve clinically meaningful weight loss at 56 weeks. Adverse events were not more likely in the early responder group v the early non-responder group from the analysis from the SCALE Obesity and Prediabetes trial.

- Le Croux C, et al. Obes Facts. 2017;10:531-44
  A post-hoc analysis to investigate the difference between those with BMI <27 to 35 kg/m^2 and those BMI >35 kg/m^2 using SCALE Obesity and Prediabetes and SCALE Diabetes trials. Significantly greater weight loss (0–56 weeks) was observed with liraglutide 3.0 mg versus placebo in all patient groups while on treatment. Similarly, for most secondary endpoints (waist circumference, HBA1c %, blood pressure and QOL) significantly greater improvements were observed with liraglutide 3.0 mg versus placebo, with no indication treatment effects differing between BMI subgroups. The safety profile of liraglutide 3.0 mg in non-diabetic participants, was broadly similar across BMI subgroups.

- Steinberg W et al. Diabetes Care 2017;40:839-48
  A secondary analyses performed on pooled data from four trials (SCALE Obesity and Prediabetes, SCALE Diabetes, SCALE Maintenance and SCALE Sleep Apnoea) (n = 5,358) investigating the impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes found that liraglutide resulted in dose-independent, reversible increases in amylase/lipase

activity, unrelated to baseline characteristics, not predicting acute pancreatitis onset. Acute pancreatitis cases were mostly mild and occurred in 9 participants in the liraglutide group whilst on treatment and 3 participants post-liraglutide treatment compared to 1 patient in the placebo group. Gallstones possibly contributed to 50% of acute pancreatitis cases. Mechanistic data are required to further advance understanding of these findings.

8.14. The Committee also noted the additional evidence below:

- Steinburg WM, et al. Diabetes Care. 2017;40:839-48
- Wilding et al. Diabetes Obes Metab. 2016;18(5):491-9
- von Scholten et al. J Diabetes Complications. 2017;31(7):1164-8

8.15. The Committee noted Canadian Agency Drug and Technologies in Health (CADTH) considered liraglutide treatment in September 2020 that they made no conclusions about the reduction of comorbidities caused by obesity in the long term and stated that reducing BMI is less meaningful than reducing comorbidities. The Committee noted the Scotland Medicines Consortium (SMC) considered liraglutide in April 2022 and had approved funding with a BMI restriction of ≥35 kg/m^2 and considered the waning effect of liraglutide. The Committee noted that NICE (England/Wales) considered liraglutide for obesity in December 2020 for those with a BMI ≥35 kg/m^2 and cardiometabolic risk factors and prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service.

8.16. The Committee considered that the proposed funded group did not align to the evidence available. The Committee considered that those that can reduce their weight from obese to normal weight would stand to benefit significantly from treatment but would not be included within the criteria despite the evidence of benefit in this group. The Committee considered those proposed for funding would remain severely obese even after a 5-10% reduction in weight and would remain at risk of cardiometabolic and physical complications related to obesity. The Committee considered that there was no evidence or clear rationale for the selection of those with a BMI ≥55 kg/m^2 as a group for funding. The Committee considered the proportion of those included in the SCALE trial with a BMI ≥50-55 kg/m^2 was not specified and efficacy in this group might be incorrectly extrapolated from those with significantly lower BMI and therefore ability to exercise. The Committee considered that the second of the proposed groups for funding (for Māori and Pacific peoples with a BMI ≥50 kg/m^2, with high cardiovascular risk and without diabetes) was not supported by evidence due to the lack of inclusion in the SCALE trial. However, the Committee considered that there was no reason to suggest that Māori and Pacific would not benefit from treatment.

8.17. The Committee considered that those at risk of developing obesity and subsequent comorbidity, would be less likely to be able to access these agents on the private market.

8.18. The Committee considered that those people that respond to liraglutide may expect to continue treatment despite the lack of evidence, past 56 weeks for those without prediabetes, and 160 weeks for those with prediabetes. The Committee considered this reasonable given the evidence of rebound weight gain during the 12 week off-drug follow up but considered that there was no long-term evidence to support this. The Committee considered that the 3 mg dose (maximum dose) of liraglutide was the appropriate dose to provide meaningful weight loss and that lower doses would be less likely to offer meaningful benefit.

8.19. The Committee noted that the diet and exercise intervention for all arms of the SCALE trial consisted of diet and exercise counselling up to week 68 and advice to increase physical activity up to 150 minutes a week, with pedometers provided to monitor, with a 500kcal reduction below individualised energy requirements with recommended

macronutrient distribution and a 3-day food diary dispensed for completion every second month. The Committee considered that this evidence showed that the combination of diet, exercise and liraglutide achieved the weight loss outcome but that efficacy of liraglutide alone without significant diet and exercise intervention was not clear. The Committee considered that the end point measuring weight loss was potentially confounded by the Hawthorne effect where behavioural change in participants enrolled in a weight loss trial with a heavily medicalised diet and exercise intervention may not correlate to the real-world behaviour change, even with medicalised diet and exercise intervention, as provided in the SCALE trial. The Committee considered that extrapolating the observed effect of liraglutide in addition to diet and exercise in a medical framework creates significant uncertainty as to the effectiveness in the absence of diet and exercise interventions. The Committee considered that real-world data with New Zealand population recruitment would indicate the efficacy in a New Zealand context.

8.20. The Committee considered other examples of funded treatments where appropriate wrap around services were not provided, such as many mental health indications or opioids for chronic non-cancer pain. The Committee considered that the evidence for efficacy varied but those treatments were still funded. The Committee considered that this indicates a need for better coordination in response across the sector for these issues.

8.21. The Committee considered that there was no coordinated national planning of obesity services available in New Zealand. The Committee considered the provision of diet and exercise services in New Zealand, such as Green Prescription, is variable across the country. The Committee considered the potential barriers to accessing funded liraglutide, as proposed, were the cost of health care or service and cost of prescription, meeting the eligibility criteria, responding, and tolerating liraglutide 3 mg dose, being motivated to continue treatment and having sufficient support and/or financial means and opportunity to reduce calorie intake and increase exercise. The Committee considered the cost of some interventions available to increase exercise or reduce calorie intake (eg a gym membership or training or the cost of vegetables and fruit) could be prohibitive to those on lower incomes, who are already inequitably burdened by obesity. The Committee considered that Māori and Pacific peoples are more likely than non-Māori, non-Pacific peoples to live in areas of greater socioeconomic deprivation, thus increasing these inequities. The Committee considered that of services for diet and exercise interventions should be delivered in a culturally appropriate way to enhance their impact in priority groups.

8.22. The Committee noted bariatric surgery as an alternative for weight loss and considered that bariatric surgery is an effective treatment of obesity, although not all of those who receive bariatric surgery are able to maintain the post-operative weight loss. The Committee considered that access to funded bariatric surgery differed throughout the country. The Committee considered these inequities extended to the psychological, nutrition and physiotherapy support services available to people post-operatively. The Committee considered that those with type 2 diabetes would be of highest priority for public funded bariatric surgery. The Committee considered that people in the proposed group for funding (BMI ≥55 kg/m^2 and ineligible for funded bariatric surgery) were likely to have additional cardiometabolic comorbidities that could make them eligible for bariatric surgery, if they met the weight eligibility criteria. The Committee considered that the use of liraglutide as a bridge to publicly funded bariatric surgery for those that qualify under all other requirements could allow this group surgery access, including those with type 2 diabetes. The Committee considered this to be a very small group of people.

8.23. The Committee also considered that the use of a higher BMI alone to assess cardiometabolic risk, has been based on the body composition of people of European ethnicity and their risk profiles and has not been validated in other population groups and therefore may not be generalisable across the latter. The Committee considered that body composition for Māori and Pacific peoples is different to European body composition (Rush E, et al. N Z Med J. 2004;117:U1203) and that the use of BMI in Māori and Pacific

peoples is not validated for the assessment of cardiometabolic risk because of multiple other confounders. The Committee considered the use of waist circumference to be a potential alternative for BMI and noted there was a significant reduction in waist circumference in the SCALE Prediabetes and Obesity trial in both the 160 week and the 56 week follow up but also noted that this was not including Māori or Pacific peoples. The Committee considered the significance of 5% weight loss, as shown in SCALE trials, in Māori and Pacific peoples compared to Europeans to be unknown based on the information presented.

8.24. The Committee considered there would be a class effect across the GLP-1 agonists as weight loss treatments. The Committee considered that although there are no comparison trials across the class for weight loss effect there was evidence for weight loss for liraglutide, semaglutide and dulaglutide. The Committee considered that there was likely a hierarchy of efficacy for weight loss within the class. The Committee noted the current global supply issues due to increased demand and considered that those with diabetes should be prioritised over those using GLP-1 agonists for weight loss only due to the serious complications associated with untreated diabetes. The Committee considered that restricting the use of liraglutide for weight loss to those without type 2 diabetes to be excluding a high needs group. The Committee noted that dulaglutide was available for those with type 2 diabetes (HbA1c ≥53mmol/mol) but that some people with type 2 diabetes, particularly recently diagnosed, may not meet the dulaglutide criteria or proposed liraglutide criteria thus excluding a potentially high needs group from funding of any GLP-1 agonist.

Suitability

8.25. The Committee considered that the daily injection formulation of liraglutide was less desirable than weekly injectable GLP-1 agonists. The Committee also considered the potential cost and environmental impact of needles and sharps disposal as the currently funded pen needles are funded for use with insulin only. The Committee noted that in the application pen needles and sharps disposal bins were to be provided by the supplier at no cost to the patient.

Cost and savings

8.26. The Committee considered the uptake in year one would be higher than assumed by Pharmac staff due to potential direct to consumer marketing and the significant uptake shown with semaglutide in the US.

8.27. The Group considered the potential impacts of this treatment on bariatric surgery waiting lists to be minimal as the demand for bariatric surgery is far higher than the supply (estimated 68 funded surgeries in the South Island annually, number of funded surgeries unavailable for the North Island). The Committee also considered that neither of the options, liraglutide treatment or bariatric surgery, are benign; both are potentially associated with morbidity, and in the case of bariatric surgery also potential mortality.. The Committee also considered that post-operative weight loss also often requires surgical removal of excess skin with considerable associated downstream costs.

Summary for assessment

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

Population	Group 1 – People who are obese (BMI ≥55 kg/m2); aged between 35 and 44 years old, unable to qualify for bariatric surgery, do not have type 2 diabetes and have pre-existing cardiovascular disease or high cardiovascular risk	Group 2 – People of Māori or Pacific ethnicity with obesity (BMI of ≥50 kg/m2), aged between 35 and 54 years old, who do not have type 2 diabetes and have pre-existing cardiovascular disease or high cardiovascular risk
Intervention	Liraglutide subcutaneous injection titrated weekly by 0.6 mg up to 3 mg to improve gastrointestinal tolerability plus diet and exercise. Week 1: 0.6mg/day Week 2: 1.2mg/day Week 3: 1.8mg/day Week 4: 2.4mg/day Week 5: 3mg/day	
Comparator(s) (NZ context)	Diet and exercise	
Outcome(s)	***Surrogate outcomes (SCALE trial outcomes over 3 years)*** Treatment response - weight loss >5% Prediabetes reversal Percent weight loss ***Clinical outcomes extrapolated from surrogate outcomes*** Onset of type 2 diabetes Health related quality of life Mortality	
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.		

9. Eribulin for the treatment of locally advanced or metastatic breast cancer (progression following at least two lines of chemotherapy)

Application

9.1. The Committee reviewed the consumer application for eribulin in the treatment of locally advanced or metastatic breast cancer which has progressed following at least two lines of prior chemotherapy.

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

Recommendation

9.3. The Committee **recommended** that eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed following two prior lines of chemotherapy be **declined.**

9.4. In making this recommendation, the Committee noted:

9.4.1. the significant health need of people with advanced or metastatic breast cancer, particularly for Māori and Pacific peoples;

9.4.2. that the evidence was conflicting and of low quality and that the results were not generalisable to the New Zealand population demographic;

9.4.3. the less-favourable adverse event profile for eribulin;

9.4.4. the minimal evidence of benefit from eribulin for the requested population.

Discussion

Māori impact

9.5. The Committee discussed the impact of funding eribulin for the treatment of breast cancer on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori are significantly disproportionately represented and that approximately 5.8% of wāhine Māori with breast cancer are diagnosed at an advanced or metastatic stage. The Committee also noted that breast-cancer specific survival (ie only including those who died of breast cancer) was 84% at 10 years for wāhine Māori, compared to 87% for those of European ethnicity (Te Rēhita Mate Ūtaetae - Breast Cancer Foundation National Register 2003-2020 report).

Background

9.6. The Committee noted the application from Breast Cancer Aotearoa Coalition (BCAC) for the use of eribulin for the treatment of individuals with locally advanced or metastatic breast cancer (HER-2 negative and triple negative breast cancers) who have progressed after at least two chemotherapeutic regimens for advanced disease. The Committee noted that eribulin has not been previously considered for any indication.

Health need

9.7. The Committee noted that advanced breast cancer includes both locally advanced and metastatic breast cancer and is classified as being Stage IV. It is the most advanced stage of breast cancer and that breast cancers can contain any of the three major receptors often found in breast cancer: oestrogen receptor alpha (ERα), progesterone receptor (PR), or human epidermal growth factor (HER2) receptor. The Committee noted that triple negative breast cancer (TNBC) cells do not present with any of the three receptors.

9.8. The Committee noted that according to a 2018 report by Breast Cancer Foundation NZ, approximately 350 New Zealanders are diagnosed with advanced breast cancer per year. The Committee noted that it is unclear if this also includes those who progress to an advanced stage of disease following an earlier diagnosis. The Committee noted that approximately 84% of breast cancers are HER2-negative, equating to 294 of the advanced breast cancers diagnosed annually. The Committee noted that men can also develop breast cancer but considered that the numbers were uncertain.

9.9. The Committee noted that approximately 5.8% of wāhine Māori living with breast cancer are diagnosed at an advanced or metastatic stage, compared to 4.7% of those of European ethnicity (Breast Cancer Foundation National Register 2003-2020 report). The Committee noted that the proportion of Pacific women diagnosed at an advanced or metastatic stage is even higher, at 10.2%. The Committee noted, however, that the referenced Beast Cancer Foundation report did not have complete national data for the time period reported, thus the true epidemiology of advanced breast cancer is New Zealand may be slightly different to what is reported.

9.10. The Committee noted that the ten-year survival for breast cancer overall was 86%; 92% for those with ER+/HER2-negative disease, and 79% for TNBC (Breast Cancer Foundation National Register 2003-2020 report). The Committee noted that the median survival after a diagnosis of stage IV breast cancer in New Zealand is 16 months.

9.11. The Committee noted that individuals with ER+/HER2-negative stage IV breast cancer are typically treated with a CDK4/6 inhibitor, followed by fulvestrant upon progression of disease, with further lines of chemotherapy if prior treatments have failed, or if the disease progresses further. The Committee noted that for individuals with TNBC, there are fewer treatment options, limited to chemotherapy, anthracycline or taxane therapy.

9.12. The Committee noted that the recommended dose of eribulin (as the ready to use solution) is 1.4 mg/m2 which should be administered intravenously over two to five minutes on Days 1 and 8 of every 21-day cycle. The Committee also noted that eribulin may also be administered by intravenous bolus over two to five minutes via a side port of a freely flowing IV infusion.

Health benefit

9.13. The Committee noted that eribulin mesilate is a halichondrin B-based, microtubule dynamics inhibitor which exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage as well as effecting tumour vasculature remodelling. The Committee noted that eribulin had not yet been granted New Zealand regulatory approval at the time of the meeting, but that an application had been made to Medsafe.

9.14. The Committee noted that individuals for whom eribulin is recommended for the treatment of their locally advanced or metastatic breast cancer and who have progressed after at least two chemotherapeutic regimens for advanced disease, should have had an anthracycline and a taxane included in either the adjuvant or metastatic setting unless these were contraindicated.

9.15. The Committee noted the following clinical evidence for the use of eribulin in the treatment of locally advanced or metastatic breast cancer:

9.15.1. Cortes et al. Lancet. 2011;377:914-23 (EMBRACE - study 305): an open-label phase III randomised trial of eribulin versus treatment of physicians choice (N=762) in the treatment of women with heavily pre-treated locally recurrent or metastatic breast cancer (2-5 previous chemotherapy regimens). 16% of participants in the trial were HER2-positive. Overall survival improved for those treated with eribulin (13.1 months versus 10.6 months with physicians' choice; p=0.041), but patients treated with eribulin experienced more fatigue and neutropenia. The median progression free survival was 3.7 months with eribulin versus 2.2 months with physicians' choice, and the objective response rate was 12% versus 2%, respectively. The occurrence of serious adverse events did not differ between the two groups.

9.15.2. Kaufman et al. J Clin Oncol. 2015;33:594-601 (Study 301): an open-label randomised phase III trial of eribulin versus capecitabine in the treatment of women with breast cancer with up to two prior chemotherapy regimens for those with advanced or metastatic disease (N=1102). 31.5% of participants in the trial were HER2-postive. There were not statistically significant differences between treatment arms for overall survival, progression free survival, adverse events, or changes in quality of life.

9.15.3. Twelves et al. Breast Cancer Res Treat. 2014;148:553-61: a pooled analysis of studies 301 and 305 by HER2 and TNBC status requested by the European Medicines Agency. The median overall survival in the intention to treat population was 15.2 months in the eribulin arm compared with 12.8 months in the control arm (HR 0.85; P =

0.003) with no statistically significant differences between subgroups. For patients with TNBC, median survival was 4.7 months longer in patients treated with eribulin than in those who received control (median OS: 12.9 vs 8.2 months; HR 0.74; P = 0.006). The trend towards improvement for those with ER+ or HER2-negative breast cancer did not appear to translate into a trend toward benefit for patients with both ER+ and HER2-negativity.

9.15.4. Pivot et al. Breast Cancer. 2018;25:370-4: a post-hoc subgroup analysis of her2-negative participants from study 301. The study reported a median overall survival of 16.1 months for the eribulin treated group versus 13.5 months in the capecitabine treated group (p=0.026), however, the capecitabine treated group had a slightly higher burden of disease at trial initiation.

9.15.5. Cortes et al. Breast Cancer Res Treat. 2015;154:509-20: a quality-of-life analysis from study 301 which reported higher rates of nausea, vomiting and diarrhoea in the capecitabine group, and worse mean scores for systemic therapy side-effects and clinically meaningful worsening of systemic therapy side effects such as dry mouth, altered taste, irritated eyes, feeling generally ill, headaches, and hot flushes. HER2-negative and TNBZ participants had similar scores to the overall treatment group, but time to symptom worsening was longer for TNBC patients treated with eribulin (however this was not statistically significant).

9.15.6. Yuan et al. Eur J Cancer. 2019;112:57-65: an open label phase III randomised trial of eribulin versus vinorelbine for the treatment of Chinese women with breast cancer and locally recurrent or metastatic disease and 2-5 prior chemotherapeutic regimens (N=530). There was a statistically significant improvement in progression free survival in the eribulin group (HR 0.88; P=0.036), however median progression free survival was 2.8 months in both treatment arms. There was not statistically significant difference in overall survival between treatment group. Grade three or higher adverse events were more frequent in the eribulin group, but treatment discontinuations due to adverse events were more common in the vinorelbine group.

9.15.7. Voutsadakis IA. Anticancer Drugs. 2017;28:557-64: a systematic review and pooled analysis of eribulin in the treatment of metastatic breast cancer. There were no statistically significant improvements in response rate, clinical benefit rate, progression free survival or overall survival.

9.15.8. Chabot et al. Curr Med Res Opin. 2020;36:2025-36: a systematic review of real-world effectiveness of eribulin in the treatment of metastatic breast cancer. Median overall survival for patients treated with eribulin ranged between 6.9 and 28.0 months, and median progression free survival for patients treated with eribulin varied from 2.3 to 14.7 months. For those with TNBC, median overall survival ranged from three to 23 months. The authors concluded that while several chemotherapy agents are available, the best sequence of treatment is unknown.

9.15.9. Tanni et al. Crit Rev Oncol Hematol.2021;163:103375: a systematic review and meta-analysis of eribulin monotherapy or combination compared to non-eribulin based regimens therapy for metastatic breast cancer. Her2-positive patients were included in the analysis. Pooled results from both randomised clinical trials and cohort studies demonstrated statistically significant benefit with eribulin for overall survival.

9.15.10. Zhao et al. BMC Cancer.2021;21:758: a network meta-analysis of eribulin monotherapy or combination therapy non-eribulin containing regimens for locally advanced or metastatic breast cancer. In HER2-negative groups, those treated with eribulin were reported to have statistically significantly longer overall survival compared with capecitabine.

9.15.11. Goodin et al. Am J Health Syst Pharm. 2015;72:2150-6: Pooled analysis of phase II and III clinical trials investigating the safety and tolerability or eribulin in the treatment of metastatic breast cancer. Dose delays were most commonly due to neutropenia (19.4%), leukopenia (4.0%), peripheral neuropathy (3.0%), asthenia (2.4%), pyrexia (2.4%), and anaemia (1.5%). Treatment was discontinued in 12.3% of patients due to treatment-emergent adverse events. Grade 3 or 4 treatment-related adverse events seen in 63.9% of patients. Eribulin was generally well tolerated, however the populations included in the study had varying ECOG scores.

9.15.12. Muss et al. Oncologist. 2014;19:318-27: Pooled analysis of three studies which investigated the effect of age on eribulin treatment. Overall survival, progression free survival, objective response rate, clinical benefit rate and tolerability was the same across all age groups (<50 to 70 years and over).

9.15.13. Pedersini et al. J Gariatr Oncol. 2020;11:976-81: A pooled analysis of clinical trial and real-world data investigating the efficacy of eribulin in older patients (70 years or over) with breast cancer. Although there was a wide range of toxicities reported, treatment of older patients was feasible.

9.15.14. Miyoshi et al. Breast Cancer. 2020;27:706-15: A post-hoc analysis of the EMBRACE study investigating predictors of overall survival. The authors reported that baseline absolute lymphocyte count may be an independent predictor of longer overall survival in eribulin treated metastatic breast cancer patients.

9.15.15. Aogi et al. Ann Oncol. 2012;23:1441-8: A phase II study of eribulin in Japanese patients with heavily pre-treated metastatic breast cancer which reported that eribulin was safe and well tolerated.

9.15.16. Fukada et al. Breast Cancer Res Treat. 2021;190:425-34: single-arm, multicentre, Phase II prospective study of patients with locally advanced breast cancer aged 20 years or older who received eribulin following treatment with anthracycline and taxane. No benefit with eribulin was reported.

9.15.17. Park et al. Cancer Res Treat. 2017;49:423-9: multicenter, open-label, single-arm, phase IV study of locally advanced or metastatic breast cancer patients in Korea treated with eribulin following anthracycline and taxane. Eribulin was reported as safe and well tolerated.

9.16. The Committee noted that the manufacturer and supplier of eribulin was heavily involved in all stages of the EMBRACE, Study 301, and Yuan et al. trials and considered this cast significant uncertainty over the validity of the results reported from these trials. The Committee considered that, in general, the evidence for benefit of eribulin in locally advanced or metastatic breast cancer was of average strength and quality. The Committee also considered that the studies were not generalisable to the New Zealand population, as the vast majority of participants in the trial were Caucasian.

9.17. The Committee noted that international guidelines recommend eribulin in the treatment of ER+/HER2-negative and TNBC breast cancers. The Committee noted that individuals with HER2-positive breast cancer have more options with HER-2 targeting therapies such as trastuzumab and trastuzumab-emtansine. The Committee noted that ESMO guidelines (Ann Oncol 2021;32:1475-1495) for TNBC treatment includes eribulin as a third line of treatment option. The Committee noted that in New Zealand there is at least one funded option in each treatment arm of the ESMO guidelines.

9.18. The Committee noted that progression free survival is a measure of biological activity, and not a clinical efficacy measure. The Committee considered that people living with cancer want to achieve clinically meaningful beneficial effects on their disease related symptoms, their ability to carry out normal activities, and on their overall survival.

9.19. The Committee considered that, overall, it is unclear if eribulin provides any additional benefit over what is currently available, and that the safety profile of eribulin is not favourable compared to available chemotherapies. The Committee noted that there was limited evidence for benefit for people with TNBC or HER2-negative disease specifically.

Suitability

9.20. The Committee noted that eribulin would require compounding by a third-party compounder or within an aseptic cytotoxic compounding facility and that not all hospitals have these facilities Members considered that there may be only one hospital in the country with compounding facilities. They noted that once compounded, eribulin has a shelf life of approximately two weeks. The Committee considered that infusion with eribulin would also increase the burden on infusion centres and facilities.

9.21. The Committee noted that treatment with eribulin would require travel to an infusion service/oncology unit and this may not be feasible for people living in areas where these services are not readily available.

Cost and savings

9.22. The Committee considered that the number of eligible individuals per year is likely closer to the Cancer Treatments Subcommittee (CaTSoP; now the Cancer Treatments Advisory Committee)'s upper estimate of 400 (April 2019), but noted that it is unknown how many would advance to metastatic or advanced disease after their initial diagnosis of breast cancer. The Committee considered that eribulin would represent an extra line of treatment to the current treatment paradigm, therefore there would be no cost offsets.

Summary for assessment

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

Population	Individuals with locally advanced or metastatic breast cancer, who are HER2-negative or triple negative and have progressed after at least two lines of therapy.
Intervention	Eribulin, 1.4 mg/m2 administered intravenously on days 1 and 8 of every 21-day cycle, until disease progression.
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Uncertain improvement in PFS (0 – 1.5 months gained, EMBRACE and Study 301) and OS (1-3 months, EMBRACE and Study 301)

Table definitions:

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

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

Comparator: 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).

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

10. Sodium + potassium + magnesium + chloride + acetate + gluconate + mannitol + bicarbonate + lidocaine + sulfate - to induce cardiac stasis and to protect the myocardium during open-heart surgery

Application

10.1. The Committee reviewed the application for del-Nido cardioplegia to induce cardiac stasis and protect the myocardium during open heart surgery.

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 del-Nido cardioplegia (Biomed) be listed with a **high** priority.

10.4. The Committee noted that the listing of del Nido cardioplegia would provide another useful cardioplegia option, which would have a high utility in certain cardiac procedures.

Discussion

Māori impact

10.5. The Committee discussed the impact of funding del-Nido solution for the induction of cardiac stasis on Māori health areas of focus and Māori health outcomes. The Committee considered that Māori have higher rates of heart disease and have higher exposure to cardiovascular risk factors such as diabetes, smoking and obesity. The Committee considered although del-Nido solution was not a direct component in reduction of cardiovascular and cardiac risk factors it could be used in the surgical treatment of heart disease that disproportionately affects Māori.

Background

10.6. The Committee noted that cardioplegia is an electrolyte solution that is used to maintain cardiac arrest, prevent dysrhythmias, avoid myocardial necrosis, deliver substrates, and wash away metabolic waste. The Committee noted that del-Nido solution is a blood cardioplegia, which is superior to crystalloid solutions.

10.7. The Committee noted that del-Nido cardioplegia solution is used to induce stasis in the myocardium during cardiac surgery and is currently funded in hospitals as it is able to be extemporaneously compounded from funded components. The Committee noted that this application was for an additional listing for Biomed's formulation of del-Nido solution as it was not funded as an extemporaneously compounded product when purchased from a manufacturer.

Health need

10.8. The Committee considered that although there was no unmet health need for this application, Māori and Pacific peoples have higher rates of heart disease and have higher exposure to cardiovascular risk factors such as diabetes, smoking and obesity. The Committee considered although del-Nido solution was not a direct component in reduction of cardiovascular and cardiac risk factors it could be used in the surgical treatment of heart disease that disproportionately affects Māori and Pacific peoples.

Health benefit

10.9. The Committee noted that del-Nido solution is a long acting cardioplegia with a duration of effect of 90 minutes compared to 20 minutes for the commonly used Buckberg solution. The Committee considered the benefit of del-Nido solution to be a reduction in the frequency of re-infusion of the cardioplegia and a decrease in cross-clamp time. The Committee considered that outcomes such as reductions in postoperative, atrial fibrillation, renal failure or low left ventricular ejection fraction did not have a strong association with decreased cross-clamp time, although noting evidence that cross-clamp time under 150 minutes may be associated with a lower risk of postoperative events (Nissinen et al. Perfusion 24 (5): 297-305).

10.10. The Committee considered that the wash out period required for del-Nido solution would be longer than shorter acting cardioplegia. The Committee considered that duration of effect is a factor in the selection of cardioplegia solution and depends on the pathology and nature of the surgery as the complexity affects the ability of the solution to reach the target areas in the heart. The Committee considered that such factors would be considered by the clinicians involved in the procedure to make an appropriate choice for the individual they are treating.

Suitability

10.11. The Committee noted that the current stability of the extemporaneous product was one month stored at 2-8 ºC. The Committee noted that the application was for del-Nido solution produced by Biomed with a 6-month expiry and able to be stored at room temperature. The Committee noted that this was not a Medsafe approved product and if funded would be supplied under Section 29. The Committee considered that previous recommendations for other therapeutics were subject to Medsafe approval however, considered that manufacturers of product are unlikely to seek Medsafe approval. The Committee considered the risk of using an unregistered product to be low for those likely to be using this product.

10.12. The Committee noted that it has been difficult for hospitals to predict the amount of del-Nido solution stock that might be required over the past few years as the COVID-19 pandemic has impacted surgical operating times. The Committee considered a longer expiry could help mitigate this issue. The Committee considered there would be less waste, reduced time needed for compounding and easier storage with the 6-month expiry product. The Committee considered that this solved a Te Whatu Ora infrastructure problem addressing both storage and time needed to compound issues.

Cost and savings

10.13. The Committee considered that an additional 10 minutes per hour of direct surgery time was saved using del-Nido (long acting) cardioplegia but considered that total time in theatre is impacted by many additional factors (preparation time, anaesthesia time, surgical team availability, blood testing delays, equipment function etc) and the impact of use of del-Nido solution on total theatre time is likely to be minimal.

10.14. The Committee considered that use of del-Nido cardioplegia with longer duration storage time would largely be confined to a subset of patients undergoing cardiac surgery, mainly in the Auckland and Waikato Te Whatu Ora districts. The Committee considered solution availability and familiarity could result in more widespread use over time. The Committee considered that del-Nido cardioplegia is not currently used for paediatric or adult congenital cardiac surgery, and current use was mainly in the adult non-congenital cardiac surgical setting. The Committee considered that del-Nido cardioplegia would be an additional option to the currently available cardioplegia solutions and may not be the preferred cardioplegia in all Te Whatu Ora districts.

Summary for assessment

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

Population	People undergoing cardiac surgery, requiring use of a cardioplegia solution to induce cardiac stasis.
Intervention	Biomed del-Nido cardioplegia solution
Comparator(s) (NZ context)	Extemporaneously compounded del-Nido solution
Outcome(s)	No significant differences in overt health benefits for risks associated with using one cardioplegia solution over another Potential for improved surgical patient flow in operating rooms (as a nominal cost saving to net health sector costs) Potential for improved availability of solution with a longer shelf life (as a nominal cost saving) Reduction in cross-clamp time (with uncertain but potential clinical benefit)
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.	

11. Physostigmine – moderate to severe simultaneous central and peripheral anticholinergic toxicity when the toxicity is only due to anticholinergic poisoning

Application

11.1. The Committee reviewed the clinician application for physostigmine for the treatment of moderate to severe central and peripheral anticholinergic toxicity.

11.2. The Committee also noted correspondence in support of the funding of physostigmine from the New Zealand National Poisons Centre.

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

Recommendation

11.4. The Committee **recommended** that for physostigmine for the treatment of moderate to severe central and peripheral anticholinergic toxicity be listed with a **high** priority on Schedule H of the Pharmaceutical Schedule (Hospital Medicines List).

11.5. In making this recommendation, the Committee considered:

- The high unmet health need for those experiencing moderate to severe central and peripheral anticholinergic toxicity, noting the limitations of current agents in treating central anticholinergic toxicity.
- The evidence which demonstrated that physostigmine provides a health benefit in those experiencing moderate to severe central and peripheral anticholinergic toxicity.
- The suitability of physostigmine as an IV infusion that can be titrated according to the individual's response.
- The potential for physostigmine to reduce health sector resource use by decreasing the length of hospital stay, reducing risk of intubation, and reducing the risks associated with use of benzodiazepines.

Discussion

Māori impact

11.6. The Committee discussed the impact of funding physostigmine for the treatment of moderate to severe central and peripheral anticholinergic toxicity on Māori health areas of focus and Māori health outcomes. The Committee considered the impact of anticholinergic poisonings on Māori health outcomes to be significant. The Committee noted that in 2018/9 Māori comprised 21.3% of all discharges for poisonings by psychotropic medicines. The Committee noted that the number of discharges for Māori patients increased by an average 8% per year between 2013 and 2019, which was slightly higher than the average increase of 5% per year observed for total discharges over this same time period (Ministry of Health. National Minimum Dataset. 2021). The Committee noted that there is a lack of published health research on the impact of toxicity on Māori health outcomes in New Zealand and consequently no further evidence has been identified in this area.

Health need

11.7. The Committee noted that anticholinergic toxicity is characterised as peripheral, central, or both peripheral and central. The Committee noted that examples of classes of medications with anticholinergic properties include antihistamines, tricyclic antidepressants, sleep aids, cold preparations, and certain recreational drugs. The Committee noted that other specific medications which may exhibit anticholinergic effects include benztropine, olanzapine, scopolamine, and atropine, and that significant anticholinergic toxicity has also been observed after the topical application of some eye drops, including cyclopentolate eye drops. The Committee noted that many plants, such

as jimson weed (*Datura stramonium*) and deadly nightshade (*Atropa belladonna*), may produce anticholinergic toxicity (Su et al. UpToDate. Last updated Aug 2021).

11.8. The Committee noted that most anticholinergic poisonings where physostigmine may be indicated are likely to occur due to the use of psychotropic medicines. The Committee noted that in 2018/9, there were 4,832 publicly funded hospital discharges for poisonings by psychotropic medicines in New Zealand (ICD codes T42, T43 and T44). The Committee noted that the mean length of stay for these hospitalisations ranged between 1.5 to 2.2 days and that, of the reported discharges, 3,212 (78.9%) involved female patients (Ministry of Health. National Minimum Dataset. 2021). The Committee noted that using ICD codes as a marker of physostigmine usage will likely provide a significant overestimation of cases where antidote treatment for the poisoning is/was required. The Committee were also made aware that the New Zealand National Poisons Centre received approximately 400 phone calls regarding anticholinergic toxicity since 2017, and that 77 of these cases required toxicologist consultation. The Committee considered that discharge patterns closely reflect patient age distributions on commonly prescribed medicines with anticholinergic effects such as olanzapine, with a peak in those aged 10 to 30.

11.9. The Committee noted that in 2018/9 there were 170 discharges for poisonings by psychotropic drugs among Pacific peoples, which represented roughly 3% of all discharges for poisonings by psychotropic drugs that year. The Committee noted that the number of discharges for Pacific peoples increased by an average 11% per year between 2013 and 2019 (Ministry of Health. National Minimum Dataset. 2021). The Committee noted that this was significantly higher than the annual increases observed for total discharges of 5%. The Committee also noted that discharge numbers for Pacific peoples should be interpreted with caution due to small patient numbers.

11.10. The Committee noted that signs of severe anticholinergic toxicity include effects on the central nervous system (CNS) such as anxiety, agitation, dysarthria, confusion, disorientation, visual hallucinations, bizarre behaviour, delirium, psychosis (usually paranoia), coma, and seizures. The Committee considered that patients with CNS toxicity require closer observation and more intensive care. The Committee noted that central effects often develop concomitantly with peripheral effects however may persist or manifest after peripheral effects resolve. The Committee also noted that some individuals may present with more subtle findings of anticholinergic toxicity such as confusion or an alteration in their mental state.

11.11. The Committee noted that there is no current antidote for central anticholinergic toxicity available in New Zealand and considered that the current treatment paradigm is limited. The Committee considered that management of anticholinergic toxicity is based on supportive care until both peripheral and central effects of anticholinergic toxicity adequately subside. The Committee considered that neostigmine is available for treatment of anticholinergic-induced ileus in cases of anticholinergic syndrome, but as it does not cross the blood brain barrier, this will only reverse peripheral effects (TOXINZ. Anticholinergic Toxicity [accessed 5 Oct 2022]). The Committee considered that intensive monitoring over several days is required for associated life-threatening conditions such as seizures, dysrhythmias, and hyperthermia. The Committee considered that activated charcoal can be used prior to the onset of significant symptoms if ileus is not present, however the patient's psychological state may impede decontamination measures.

11.12. The Committee considered that benzodiazepines are used for the management of agitation, delirium, or seizures, and barbiturates may be given if seizures are refractory. The Committee considered that benzodiazepines carry a higher risk of intubation compared with using physostigmine, and have complications especially when given in high doses, as is sometimes required in anticholinergic toxicity. The Committee noted that physostigmine can reverse anticholinergic delirium, is associated with decreased agitation, less complications, and shorter recovery time compared with benzodiazepines.

11.13. The Committee noted that this proposal also aligns with the government priority to improve management of long-term conditions, noting that some patients with chronic mental health conditions or Parkinson's disease may be treated with anticholinergic medications and are therefore at risk of anticholinergic toxicity.

Health benefit

11.14. The Committee noted that physostigmine is a reversible cholinesterase inhibitor which increases the concentration of acetylcholine at the sites of cholinergic transmission. The Committee noted that physostigmine can reverse both central and peripheral anticholinergic symptoms as it crosses the blood-brain barrier (PubChem. National Centre for Biotechnology Information. Physostigmine [accessed 5 Oct 2022]). The Committee noted that physostigmine is not Medsafe approved, and that regulatory approval has not been sought from Medsafe for the requested indication.

11.15. The Committee noted that the recommended dose of physostigmine in children is 0.02 mg/kg (maximum 0.5 mg) intravenously over 5 to 10 minutes, and in adults is 0.5 mg to 1 mg intravenously over 5 to 10 minutes. The Committee noted that physostigmine has a relatively short duration of action of 20 to 60 minutes (though sometimes longer), and that further carefully titrated doses may be required if severe or life-threatening symptoms recur following initial clinical response. The Committee noted that additional doses should be given with caution as repeated dosing increases the risk of adverse effects. The Committee noted that strong evidence supports the contraindication to using physostigmine in tricyclic antidepressant overdose (Schneider. Emergency Medicine News. 2003;25:44).

11.16. The Committee noted that there are two key studies which provide evidence on the health benefit of physostigmine in the treatment of central and peripheral anticholinergic toxicity. The Committee considered that the patient numbers for the two key studies were small, however that this is to be expected in this population.

11.16.1. The Committee noted a double blinded, randomised controlled trial including 19 patients presenting for antimuscarinic toxidrome aged ≥10 and <18 years old, with at least one central and two peripheral antimuscarinic symptoms, delirium, and moderate agitation. The Committee noted that patients were randomised to receive lorazepam (n=10) 0.05 mg/kg bolus followed by a 4-hour normal saline infusion or physostigmine (n=9) 0.02 mg/kg bolus followed by a 4-hour physostigmine infusion (0.02 mg/kg/h). The Committee noted that fewer patients receiving physostigmine had delirium after the initial bolus (44% vs 100%, P=0.01) and at the fourth hour of infusion (22% vs 100%, P<0.001) compared to patients who received lorazepam. The Committee noted that there was a significant decrease in agitation scores in the physostigmine arm compared to the lorazepam arm after the initial bolus (89% vs 30%, P=0.02), but no difference at the fourth hour of infusion (P>0.99). The Committee noted that no seizures, bradycardia, bronchorrhea, bronchospasm, intubation, or cardiac dysrhythmias were reported amongst participants (Wang et al. Clin Toxicol (Phila). 2021;59:698-704).

11.16.2. The Committee noted a retrospective study including 52 patients referred to a university hospital toxicology consultation service who were treated with physostigmine (n=30), benzodiazepines (n=22), or both for anticholinergic agitation and delirium. The Committee noted that the mean total dose of treatments was physostigmine 3.9 mg (range 0.5 mg to 13.5 mg), diazepam 53.1 mg, lorazepam 35.5 mg, and midazolam 31.7 mg. The Committee noted that physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively. The Committee noted that benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. The Committee noted that initial treatment with physostigmine resulted in a significant decrease in the incidence of agitation (P<.001) and level of central nervous system stimulation (P<.001), whereas initial treatment with benzodiazepines did not (P=0.03 and P=0.05, respectively). The Committee noted that patients treated initially

with physostigmine had a significantly lower incidence of complications (7% versus 46%; *P*<.002) and a shorter time to recovery (median, 12 versus 24 hours; *P* =.004) than those treated initially with benzodiazepines. The Committee noted that there were no significant differences between these groups in the incidence of side effects (7% versus 14%; *P*=0.6) and length of stay (median, 32 versus 39 hours; *P* =0.15) (Burns et al. Ann Emerg Med. 2000;35:374-81).

11.17. The Committee noted the following additional publications reporting on the use and safety of physostigmine:

11.17.1. The Committee noted a retrospective cohort study of hospitalised patients reported to a regional poison centre system between 2003 and 2012 who received physostigmine to reverse an anticholinergic toxidrome. The Committee noted that most patients (n=182; 95.3%) had no documented adverse effects, four patients (2.1%) experienced emesis, two experienced QTc prolongation (1.0%), two experienced seizures (1.0%), and that there was a single fatality 6 hours after physostigmine administration. The Committee noted that the average initial total doses of physostigmine ranged from 1.0 mg to 1.75 mg and that most patients were admitted to the ICU (n=110; 57.6%), however, 36 (18.8%) patients were discharged directly from the ED (Arens et al. Clin Toxicol (Phila). 2018;56:101-7).

11.17.2. The Committee noted a retrospective, observational study reporting adverse events from physostigmine. The Committee noted that the study reported no serious adverse events when physostigmine was used for treating antimuscarinic toxicity in a contemporary practice (Nguyen et al. Am J Emerg Med. 2018;36:141-2).

11.17.3. The Committee noted a case study of two patients with tricyclic antidepressant toxicity who developed asystole following the administration of physostigmine to treat seizures (Pentel, Peterson. Ann Emerg Med. 1980;9:588-90).

11.17.4. The Committee noted a retrospective chart review of patients given physostigmine for likely antimuscarinic toxicity (Rosenbaum, Bird. J Med Toxicol. 2010;6:386-92).

11.17.5. The Committee noted a retrospective chart review on all adult patients administered physostigmine diagnostically over a 79-month period at a tertiary-care hospital (Schneir et al. Ann Emerg Med. 2003;42:14-9).

11.17.6. The Committee noted a case study assessing physostigmine's contraindications in cyclic antidepressant ingestions (Suchard. J Emerg Med. 2003;25:185-91).

11.17.7. The Committee noted a retrospective analysis of the use of physostigmine by toxicologists in anticholinergic toxicity (Watkins et al. J Med Toxicol. 2015;11:179-84).

11.18. The Committee noted that physostigmine was also included in the recently released New Zealand National Poisons Centre Antidote Stocking Guideline for Hospitals that Treat Poisoning Emergencies (Version 1.0, released August 2022).

Suitability

11.19. The Committee considered that physostigmine is administered intravenously, and that this is not expected to adversely impact on its use. The Committee noted that physostigmine has a shorter half-life than most benzodiazepines so additional doses may be required. The Committee considered that physostigmine dose can be titrated according to the individual's response. The Committee also noted that there is also a small risk of cholinergic toxicity with use of physostigmine if the patient has not been poisoned with an anticholinergic substance.

Cost and savings

11.20. The Committee considered that the budget impact associated with listing physostigmine is likely to be very low. The Committee considered that, if physostigmine is listed, there may be incremental pharmaceutical and administrative costs involved in ensuring availability across relevant centres in New Zealand and replenishing expired stock. The Committee considered that physostigmine may decrease length of hospital stay and ICU time, reduce the risk of intubation, reduce risks associated with use of benzodiazepines, and thereby be associated with reductions in health sector resource use.

11.21. The Committee considered that, if listed, approximately 500 poisonings per year may be treated with physostigmine. The Committee noted that this estimate was lower than the total number of publicly funded discharges for poisonings by psychotropic medicines in New Zealand reported for 2018/9. The Committee considered that most anticholinergic poisonings do not cause the level of peripheral and/or central toxicity that would require treatment with physostigmine.

Funding criteria

11.22. The Committee considered that, if physostigmine were to be funded, it is proposed that it is listed on Schedule H of the Pharmaceutical Schedule (ie the Hospital Medicines List) to be used in those exhibiting moderate to severe peripheral and central anticholinergic toxicity.

Summary for assessment

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

Population	People experiencing moderate to severe central and peripheral anticholinergic toxicity
Intervention	Physostigmine • Dosage of 0.02 mg/kg IV STAT, up to 2 mg per dose for adults and 0.5 mg per dose in paediatric patients • Smaller doses repeated after 20-30 minutes if agitated delirium occurs Treatment duration is informed by the duration of anticholinergic delirium
Comparator(s) (NZ context)	Best supportive care • Secure airway, breathing and circulation • Benzodiazepines, as required, to manage agitation and seizures • Activated charcoal if mental status is intact
Outcome(s)	Reversal of anticholinergic delirium Reduced risk of complications – lower rate of intubation

Table definitions:

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

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

Comparator: 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).

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