

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 23 & 24 May 2019

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

Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the minutes relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule

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

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Record of attendance to the Pharmacology and Therapeutics Advisory Committee Meeting May 2019

PTAC members:

Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Giles Newton Howes (excused on 24 May)
Jane Thomas (excused on 24 May from 8:30am to 8:50am)
Jennifer Martin (left meeting on 24 May at 2:00pm)
Melissa Copland
Sean Hanna (excused on 24 May from 8:30am to 9:45am)
Simon Wynn Thomas
Tim Stokes

1. Record of PTAC meeting held 21 and 22 February 2019

- 1.1. The Committee reviewed the minutes of the PTAC meeting held on **21 and 22 February** and **agreed** that the minutes be accepted.

2. Diabetes Subcommittee March 2019 meeting minutes

- 2.1. The Committee noted the record of the Diabetes Subcommittee meeting held on 19 March 2019.
- 2.2. Regarding item 6, the Committee noted recommendation 6.5 that the Freestyle Libre Flash Glucose Monitoring System be funded with a high priority. The Committee considered that it was unable to endorse a high priority recommendation based on the quality of the evidence reviewed, the absence of data demonstrating HRQoL benefits, and uncertainty regarding the level of health need given currently funded alternatives.
- 2.3. The Committee considered that Freestyle Libre was one of a number of devices with similar functionality to continuously monitor glucose levels available internationally.
- 2.4. The Committee considered that flash and/or continuous glucose monitoring technology, as with most medical device technologies, was rapidly evolving with new and incrementally updated technology continuously coming to market in relatively short time frames.
- 2.5. The Committee considered that assessment of medical devices was complex and as identified by the Diabetes Subcommittee would likely require consideration of diverse data sources.
- 2.6. The Committee considered that further evidence and information would be needed to support the benefit that continuous glucose monitoring technology could provide for New Zealand diabetes patients, particularly regarding the health-related quality of life for patients and family members, from use of continuous monitoring.
- 2.7. The Committee considered that assessment of continuous glucose monitoring technology did not fit well in the current medicines assessment framework; it may be more appropriate to seek clinical advice on device technology from individuals and groups with expertise in assessment of device technologies.
- 2.8. The Committee considered that PTAC and its Subcommittee's may not have the technical expertise to appropriately assess these devices and recommended that PHARMAC consider aligning its assessment of community devices such as continuous glucose monitoring technology and insulin pumps with the assessment framework

currently being developed for hospital devices, particularly to ensure patient safety, usability, lifespan and technology upgrades were appropriately considered and managed.

- 2.9. Regarding item 7, the Committee noted the Subcommittee's recommended Special Authority criteria for antidiabetic agents for the improvement of cardiovascular outcomes for patients with T2DM and established cardiovascular disease.
- 2.10. The Committee considered that it would be important to target these treatments to those patients who would benefit most from treatment and that the clinical preference would be for funding in populations with high risk cardiovascular disease or established cardiovascular disease (represented by a 5-year absolute cardiovascular disease risk of 20% or over).
- 2.11. The Committee considered that the distribution of New Zealand type 2 diabetes patients and cardiovascular disease risk would be critical for understanding and clearly defining this population. The Committee considered it would be appropriate for access criteria to specify which cardiovascular risk calculator should be used, but considered it reasonable that this be both a diabetes specific and New Zealand specific calculation of risk.
- 2.12. The Committee recommended that further analysis be undertaken to estimate the patient numbers likely to be impacted by the various thresholds for cardiovascular risk, and the impact of reducing the threshold to include high cardiovascular risk patients.
- 2.13. The Committee noted that there was strong evidence that SGLT-2 and GLP-1 agents improved renal outcomes, however the Subcommittee's recommended Special Authority did not explicitly include patients with renal disease without established cardiovascular disease who may benefit from treatment with these agents. The Committee recommended that additional clinical advice on appropriate criteria to define a population of people who would benefit from the renal outcomes of treatment with SGLT-2 or GLP-1 agents be sought.
- 2.14. The Committee noted and accepted the remainder of the record of the 19 March 2019 Diabetes Subcommittee meeting including the remaining recommendations; 4.35, 5.17, 5.22, 5.32, 8.4.

3. Haematology Subcommittee January 2019 meeting minutes

- 3.1. The Chair noted the need to have second PTAC member on the committee.
- 3.2. The Chair nominated PTAC member, Brian Anderson to the Haematology Subcommittee.
- 3.3. The Committee considered the record of the Haematology Subcommittee meeting held 30 January 2019. The Committee noted and accepted all the Subcommittee recommendations.

4. Immunisation Subcommittee March 2019 meeting minutes

- 4.1. The Committee reviewed the Immunisation Subcommittee minutes from the 8 March 2019 meeting.
- 4.2. The Committee noted that the Subcommittee considered additional evidence for meningococcal ACWY and meningococcal B vaccines that was not provided to the Committee when it considered meningococcal vaccines at its February 2019 meeting. The Committee noted that the Subcommittee recommendations were made based on the additional evidence considered, and accepted recommendations 3.3 to 3.6 and recommendations 4.3 to 4.6.

- 4.3. The Committee noted that the Subcommittee considered that it strongly supported the addition of a dose of hexa-valent DTaP-IPV-Hep/Hib vaccine to replace Hib at the 15 month childhood vaccination visit. The Committee requested that the Subcommittee provide more information about the evidence base for adding a dose of hexa-valent vaccine at 15 months.
- 4.4. The Committee noted and accepted the remaining recommendation of the Immunisation Subcommittee, 5.3.

5. Neurology and Mental Health Joint Subcommittee March 2019 meeting minutes

- 5.1. The Committee noted and accepted the record of the Neurological and Mental Health Joint Subcommittee of PTAC meeting held on 7 February 2019

6. Neurology Subcommittee March 2019 meeting minutes

- 6.1. The Committee noted and accepted the record of the Neurological Subcommittee of PTAC meeting held on 7 February 2019

7. Buprenorphine transdermal patches for the treatment of persistent moderate/severe pain

Application

- 7.1. The Committee reviewed correspondence requesting reconsideration of an application for buprenorphine transdermal patches for the treatment of chronic moderate/severe non-malignant pain.
- 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 the application for buprenorphine transdermal patches for persistent moderate/severe chronic non-malignant pain be **declined**, based on insufficient evidence of long-term analgesic benefit, lack of evidence regarding functional improvements and improvements in health-related quality of life, and concerns regarding diversion and possible societal harm.
- 7.4. The Committee **recommended** that PHARMAC staff consider a review of the funding of and access to opioid analgesics for chronic non-malignant pain in New Zealand and bring a discussion paper to PTAC on this matter at a future meeting.

Discussion

- 7.5. The Committee reviewed correspondence from the New Zealand Society of Anaesthetists Inpatient Pain Network requesting that PHARMAC reconsider the recommendation of PTAC that funding for buprenorphine transdermal patches be declined.
- 7.6. The Committee noted the correspondent had suggested that access to buprenorphine transdermal patches be limited to certain prescribers (anaesthetists, pain physicians and palliative care specialists) and the following patient groups;
 - Patients with difficult to control pain
 - Elderly patients with co-morbidities
 - Trauma patients with concurrent substance misuse
 - Patients requiring transitional analgesia

- 7.7. The Committee reviewed the history of prescribing opioids for use in chronic non-malignant pain, along with trends in opioid prescribing practice internationally and in New Zealand. The Committee noted [data released by the Health Quality and Safety Commission](#) and considered there was a concerning trend in the use of strong opioids, in particular the use of morphine and fentanyl patches in rest homes.
- 7.8. The Committee noted that it had reviewed an application for buprenorphine transdermal patches in 2009 and, based on the evidence at that time, recommended that buprenorphine patches be funded with a low priority. The Committee noted that in late 2017, the supplier of buprenorphine patches submitted an updated commercial proposal to PHARMAC. The Committee noted that PHARMAC staff sought the advice of the Analgesic Subcommittee at its March 2018 meeting on the likely benefits and risks of buprenorphine as an analgesic agent in the setting of chronic non-malignant pain, the benefits and suitability of a weekly buprenorphine patch, and the likely place in therapy.
- 7.9. The Committee noted that the Analgesic Subcommittee recommended that the application for buprenorphine patches for the treatment of severe chronic non-cancer pain be declined. The Committee noted that at its March 2018 meeting the Analgesic Subcommittee considered that PHARMAC should carefully consider the potential consequences of abuse, misuse, and dependence in its funding assessments of new opioid medicines, as any new funding would likely increase the total opioid market and the number of patients being treated with an opioid.
- 7.10. The Committee reviewed the pharmacology of buprenorphine. The Committee noted that patches are designed to provide a steady delivery of buprenorphine for up to 7 days up to a maximum dose delivery of 40 micrograms per hour. The Committee noted that plasma steady state concentrations are reached at day 3 of treatment and therefore considered that the patch would not be suitable for the management of acute pain. The Committee noted that there was no dose adjustment needed in renal impairment or in mild-moderate hepatic impairment.
- 7.11. The Committee considered there were a number of potentially beneficial differences in comparison to other opioid medications, including a ceiling effect on respiratory depression, no adverse effects on the hypothalamic-pituitary-adrenal axis, no induction of hypogonadism, and no clinically significant impact on QTc interval. The Committee considered, however, that much of the safety data came from animal studies and studies in healthy volunteers, rather than in the target population (ie. patients with chronic non-malignant pain).
- 7.12. The Committee noted literature provided by the correspondent, and considered in particular the following evidence regarding efficacy;
- 7.12.1. The Committee considered a systematic review of buprenorphine that included 15 trials of buprenorphine transdermal patches ([Aiyer et al. *Anaesth Analg* 2018;127:529-38](#)). The Committee noted that there were 10 positive trials, however only 1 trial demonstrated superiority over an active comparator. The Committee considered that there were a number of different formulations of buprenorphine studied, in a number of different chronic pain conditions, and that the populations were therefore heterogeneous in nature. The Committee considered that due to the variety of endpoints used and population heterogeneity a formal meta-analysis was not possible. The Committee considered an accompanying editorial ([Sun et al. *Anesth Analg* 2018;127:336-7](#)), which commented that the use of buprenorphine in chronic pain has significant implications in peri-operative analgesia as its partial agonist activity may cause reduced efficacy of other strong opioids
- 7.12.2. The Committee considered a meta-analysis of 28 randomised controlled trials comparing buprenorphine with morphine and noted that none of these studies used a transdermal presentation of buprenorphine and therefore considered that

the analysis was not relevant to the application ([White et al Br J Anaesth 2018;120:668-78](#)).

- 7.12.3. The Committee considered a randomised controlled trial investigating the comparative efficacy of transdermal buprenorphine and slow-release tramadol in the postoperative setting following single-level spinal fusion surgery ([Kim et al Eur Spine J 2017;26:2961-8](#)). The Committee considered the rationale for the use of transdermal buprenorphine in this patient cohort was unclear, as the majority of patients were unlikely to require transdermal buprenorphine for the duration prescribed in the study.
- 7.12.4. The Committee considered a randomised controlled trial investigating the efficacy of transdermal buprenorphine in neuropathic pain in comparison to placebo. The Committee considered that the treatment effect reported in this study (30% reduction in average versus baseline pain at week 12) was modest and unlikely to be clinically significant ([Simpson et al. Diabetes Care 2016;39:1493-500](#)).
- 7.13. The Committee considered literature provided by the correspondent, regarding safety of buprenorphine patches, including the following:
 - 7.13.1. The Committee considered a literature review ([Davis MP. J Support Oncol 2012;10:209-19](#)) of buprenorphine transdermal patches. The authors of the review reported that a ceiling effect was observed for respiratory depression. The Committee considered that the evidence to support this was from studies in animals and healthy volunteers and therefore would not necessarily be representative of patients with chronic non-cancer pain, particularly those taking other central nervous system depressants. The Committee considered that many patients with chronic non-cancer pain may be using other central nervous system depressants such as benzodiazepines, and this concomitant use could significantly increase the risk of respiratory depression.
 - 7.13.2. The Committee considered a retrospective analysis of 16 placebo-controlled and active-controlled, and uncontrolled studies that compared safety profiles of buprenorphine transdermal patches in older patients (≥ 65 years) with younger patients (< 65 years) ([Pergolizzi et al. Postgrad Med 2017;129:92-101](#)). The Committee considered that the data indicated that older patients were more likely than younger patients to experience adverse events associated with buprenorphine transdermal patches. The Committee considered that there would be value in comparative analysis of the safety of buprenorphine transdermal patches in older versus younger patients relative to other strong opioids, however the analysis presented was limited by the relatively small patient numbers.
 - 7.13.3. The Committee considered a retrospective cohort study comparing rates of abuse, suspected suicidal intent and fatalities with buprenorphine transdermal patches in comparison to other opioid analgesics using data from the National Poison Data System in the US ([Coplan PM et al. Postgrad Med 2017;129:55-61](#)). The Committee considered that the study was limited by the relatively low patient numbers prescribed buprenorphine versus other strong opioids. The Committee considered that using Poison Centre reporting may have led to under-reporting of events, and therefore considered caution was needed in interpreting the conclusion that there are lower rates of these events with buprenorphine transdermal patches in comparison to other opioid analgesics. In addition, the Committee considered that the majority of patients dispensed buprenorphine transdermal patches in the Poison Centre database used the patch concomitantly with other opioids and therefore that the use of the patch did not mean that patients would reduce their use of other opioids.
 - 7.13.4. The Committee considered another retrospective cohort study from the National Poison Data System in the US evaluating buprenorphine exposure in children and

adolescents ([Post S et al. Pediatrics 2018;142:e20173562](#)). The Committee considered that this analysis included other buprenorphine formulations in addition to the transdermal patch. The Committee considered that this analysis suggested a small risk of intentional and unintentional exposure in children and adolescents that would be of potential concern if buprenorphine transdermal patches were made available in New Zealand.

- 7.13.5. The Committee considered a [rapid response document](#) prepared by the Canadian Agency for Drugs and Technology in Health (CADTH) in January 2017 that provided a summary and critical appraisal of the evidence for the clinical effectiveness of buprenorphine in chronic non-cancer pain. The Committee considered the conclusion of this review was that the improvements in pain for patients with chronic non-cancer pain, from treatment with buprenorphine relative to placebo, was modest and in some studies did not meet the recognised standard for minimum clinically important significance. The Committee considered that the authors concluded that available evidence was insufficient to assess the relative harms of buprenorphine to other opioids in patients with chronic non-cancer pain, including in relation to respiratory depression.
- 7.14. The Committee considered that the evidence reviewed did not change its view that there is limited evidence of long-term analgesic benefit and functional improvements for the use of opioids, including buprenorphine transdermal patches, in the management of chronic non-malignant pain. The Committee considered that there is overwhelming evidence to suggest possible harms resulting from long term opioid use. The Committee considered that non-opioid pharmacological therapy and non-pharmacological therapies are the preferred treatment options for chronic non-malignant pain to improve functional status and health-related quality of life.
- 7.15. The Committee considered that the evidence it reviewed did not change its view that buprenorphine has a moderate abuse potential and that should buprenorphine patches be funded, there would likely be a proportion of use that would be inappropriate, including diversion and potential societal harm. The Committee considered that limiting prescribing to certain prescriber types and patient groups would be unlikely to significantly attenuate this risk. The Committee also considered that despite buprenorphine being a transdermal patch it was possible to extract the buprenorphine from the patch.
- 7.16. The Committee considered that if buprenorphine transdermal patches were to be funded, specific advice should be sought from the Analgesic Subcommittee regarding appropriate Special Authority criteria, and that prescribing should be limited to Pain Medicine Specialists and Addiction Medicine Specialists.
- 7.17. The Committee considered that the evidence and information provided by the New Zealand Society of Anaesthetists Inpatient Pain Network did not change its view on the Analgesic Subcommittee's recommendation that funding for buprenorphine transdermal patches be declined.
- 7.18. The Committee considered the current opioid epidemic in the US and Canada and the increasing problem of opioid prescribing for chronic non-malignant pain in New Zealand, despite large educational campaigns. The Committee considered that one possible way of reducing inappropriate prescribing of opioids for chronic non-malignant pain would be to consider funding and/or access restrictions on strong opioids. The Committee considered that similar considerations had been given to creating funding restrictions for antibiotics to help reduce antimicrobial resistance; however practically this had been difficult to implement due to significant regional variations in prescribing practice.

8. Fomepizole for the treatment of ethylene glycol or methanol poisoning

Application

- 8.1. The Committee reviewed the application from AFT Pharmaceuticals for fomepizole (Antizol) for the treatment of ethylene glycol or methanol poisoning.
- 8.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 8.3. The Committee **recommended** that fomepizole in the treatment of ethylene glycol or methanol poisoning be listed with a **high priority**. The Committee considered that although the evidence base for the use of fomepizole in the treatment of ethylene glycol or methanol poisoning was poor, there is a high health need in patients with this condition which disproportionately affects Māori; and the different adverse event profile of fomepizole compared to ethanol may reduce health sector costs in the treatment of these patients. The Committee considered that the priority of its recommendation should be reviewed if fomepizole would not reduce health sector costs.
- 8.4. The Committee **recommended** fomepizole be listed in the Hospital Medicines List (HML) subject to the following restrictions for use:

FOMEPIZOLE

Initiation

All of the following:

1. Either:
 - 1.1. Patient has a serum ethylene glycol or methanol concentration of greater than 20 mg/dL; or
 - 1.2. Either:
 - 1.2.1. Patient has a documented recent history of ethylene glycol or methanol ingestion with increased osmolal gap of greater than 10 mOsm/kgH₂O; or
 - 1.2.2. Both:
 - 1.2.2.1. Patient has a history of ethylene glycol or methanol ingestion; and
 - 1.2.2.2. At least two of the following:
 - 1.2.2.2.1. Arterial pH of less than 7.3; or
 - 1.2.2.2.2. Serum bicarbonate of less than 20 mmol/L; or
 - 1.2.2.2.3. Osmolal gap of greater than 10 mOsm/kgH₂O; or
 - 1.2.2.2.4. Urinary oxalate crystals present (only in ethylene glycol poisoning cases); and
2. Treatment with fomepizole will continue until the patient's methanol or ethylene glycol concentration is reduced below 20 mg/dL, symptoms have resolved, and pH has normalised.

Discussion

- 8.5. The Committee noted that poisoning from ethylene glycol or methanol results from deliberate or accidental ingestion of products containing these agents (such as antifreeze or windscreen fluid) or where they are used as an ethanol substitute (such as moonshine). The Committee noted that this poisoning can occur in adults or children and these patients may present to an Emergency Department) or General Practitioner as individual cases or as multiple cases at a time (considered to be an 'outbreak').
- 8.6. The Committee noted that the metabolites of ethylene glycol or methanol are toxic, rapidly lead to metabolic acidosis, and can cause damage to the kidneys, eyes (potentially causing blindness), central nervous system (CNS), cardiopulmonary system, and in many cases results in death.
- 8.7. The Committee noted that the applicant estimates that there are approximately 28 cases of ethylene glycol or methanol poisoning per year in New Zealand, based on data of

contacts with the National Poisons Centre (NPC) and information downloads from the poison information website, TOXINZ. The Committee considered these data sources may not capture all cases because experienced clinicians may not need to seek advice from the NPC or TOXINZ; and that Emergency Department physicians should be contacted to clarify patient numbers.

- 8.8. The Committee noted that the applicant provided hospital discharge data from 2015 to 2016 for patients who received publicly funded hospital treatment for poisoning (not only due to ethylene glycol or methanol) and that of 71 patients discharged, 22 were Māori and 3 were Pacific people, suggesting there may be disproportionate incidence in Māori.
- 8.9. The Committee noted that the current treatment for ethylene glycol or methanol poisoning in New Zealand consists of controlled intoxication with high doses of medical ethanol, intravenously administered in intensive care units (ICU) sometimes over several days and monitored by frequent testing of ethanol concentration and metabolic status (including pH and bicarbonate levels).
- 8.10. The Committee considered that ethanol is funded without restriction, readily available and its therapeutic use is well known. The Committee noted that ethanol blocks metabolism of ethylene glycol or methanol which is instead excreted in urine. Members considered there are some concerns about whether the continuous infusion of ethanol over several days can cause CNS damage.
- 8.11. The Committee noted that intubation (for patients with compromised airways) or haemodialysis (to assist with removal of agents or metabolites) may be required in some cases and considered that treatment which prevents metabolite formation could reduce or prevent the need for haemodialysis.
- 8.12. The Committee considered that management of patients being treated with ethanol can be challenging due to behavioural disturbances resulting from the induced ethanol intoxication and the need for intubation in some patients, which places a considerable demand on limited ICU beds. Members also considered it is challenging to treat patients with poisoning in rural areas with an ethanol infusion.
- 8.13. The Committee noted that fomepizole is a competitive inhibitor of alcohol dehydrogenase and that it is administered over 30 minutes every 12 hours by intravenous infusion in a hospital setting until the patient's ethylene glycol or methanol concentration is reduced below 20 mg per dL, symptoms have resolved, and pH has normalised.
- 8.14. The Committee considered that fomepizole would likely require less intensive patient monitoring than ethanol.
- 8.15. The Committee noted that fomepizole was approved by Medsafe in December 2018 for use as an antidote for ethylene glycol or methanol poisoning or for their suspected ingestion, with or without haemodialysis, and that fomepizole is included on the [World Health Organisation \(WHO\) Model List of Essential Medicines](#).
- 8.16. The Committee noted that the applicant provided the published results of two prospective observational clinical studies in patients with ethylene glycol poisoning ([Brent et al. N Engl J Med. 1999;340:832-8](#)) and with methanol poisoning ([Brent et al. N Engl J Med. 2001;344:424-9](#)). The Committee noted that these trials did not include control groups and were of low to moderate quality regarding adverse effects (rated according to the GRADE approach), however, the Committee considered that this evidence showed that fomepizole was effective in normalising acid-base status.
- 8.17. The Committee considered that it was unclear whether the adverse events (AEs) reported in each of the two studies ([Brent et al. N Engl J Med. 1999;340:832-8](#); [Brent et al. N Engl J Med. 2001;344:424-9](#)) were related to fomepizole treatment or if they were

due to the poisoning. The Committee noted the authors reported cardiovascular AEs in patients who received fomepizole and considered that these were concerning for patients with ethylene glycol or methanol poisoning who have considerable morbidity.

- 8.18. The Committee noted the results of a retrospective observational case series assessing risk factors related to poor outcome in 203 patients with methanol poisoning (of which 32 received fomepizole) reported by [Paasma et al. \(Clin Toxicol \(Philia\). 2012;50:823-31\)](#). The Committee considered the results showed that low pH, coma and inadequate hyperventilation on admission were strong predictors of poor outcome. The Committee also noted that the authors suggest ethanol and fomepizole are equally effective treatments, but the practical disadvantages of ethanol can affect its efficacy.
- 8.19. The Committee noted the results of a retrospective study of 172 patients hospitalised between 1996 and 2005 for ethylene glycol and methanol poisoning ([Lepik et al. Ann Emerg Med. 2009;53:439-50](#)). The Committee noted that the authors report more AEs occurred in patients who received ethanol (57%) than in patients who received fomepizole (12%), and that there were more severe or life-threatening AEs in patients receiving ethanol (20% and 8% respectively) than with fomepizole (5% and 2% respectively).
- 8.20. The Committee noted the results of a pharmacokinetic (PK) study of fomepizole in healthy volunteers which were reported by [McMartin et al. Clin Toxicol \(Philia\). 2012;50:375-83](#) in which the authors suggest, based on their results, that patients require an increased dose of fomepizole after 36 hours. The Committee considered this dosing regimen would be relevant to the cost of funding fomepizole.
- 8.21. The Committee noted that the results of a physiologically-based pharmacokinetic study which investigated relative exposures of fomepizole and alcohol dehydrogenase enzyme activity ([Corley and McMartin. Toxicol Sci. 2005;85:491-501](#)). The Committee considered that the authors reported that the effect of fomepizole on alcohol dehydrogenase was not clearly correlated with outcome, although theoretically it should be.
- 8.22. The Committee noted the AE data provided from two randomised, unblinded studies of fomepizole in healthy volunteers ([Jacobsen et al. Alcohol Clin Exp Res. 1988;12:516-22](#); [Jacobsen et al. J Emerg Med. 1990;8:455-61](#)). The Committee noted the authors reported gastrointestinal, CNS, cardiovascular and metabolic AEs with fomepizole.
- 8.23. The Committee noted the results of a case series of 38 patients with ethylene glycol poisoning reported by [Borron et al. \(Lancet. 1999;354:831\)](#), which suggest that fomepizole is effective and safe treatment, especially if administered early, and that fomepizole alone is sufficient therapy for patients with normal renal function and normal acid-base status.
- 8.24. The Committee also noted the evidence provided in the application to list fomepizole on the [WHO Model List of Essential Medicines](#) and considered that this provided reasonable evidence for fomepizole in this indication.
- 8.25. The Committee considered that evidence indicated that fomepizole had a different but not necessarily better AE profile compared to ethanol. The Committee considered that while there were fewer toxicities reported with use of fomepizole, significant AEs (including cardiovascular AEs) were reported in patients receiving fomepizole.
- 8.26. The Committee considered that the evidence for fomepizole was of poor quality and strength which made it difficult to draw conclusions about the benefit of fomepizole compared to ethanol. The Committee considered that the retrospective nature of the data provided some long-term data on outcomes and limited reporting of AEs, although members were uncertain of the accuracy of comparing AE data across studies.

- 8.27. The Committee considered it unlikely that there will be high-quality evidence from randomised controlled trials of ethanol compared to fomepizole in patients with ethylene glycol or methanol poisoning in future, due to the challenges in research in patients with this poisoning, since fomepizole appears to have been used preferentially for very unwell patients in some trials, and because it has already been adopted globally.
- 8.28. The Committee considered that fomepizole had similar efficacy to ethanol and that it was likely that fomepizole would benefit patients who present with severe poisoning. The Committee considered that the evidence suggests fomepizole may reduce health resource use in patients with ethylene glycol or methanol poisoning, however, it is unclear whether fomepizole would reduce the costs of managing these patients.
- 8.29. The Committee noted that health resource costs are influenced by whether patients with ethylene glycol or methanol poisoning require care in an ICU or a high-dependency unit (HDU), and whether intubation or haemodialysis is required.
- 8.30. The Committee considered that specialist advice should be sought from groups such as intensive care unit physicians, emergency department physicians, toxicologists and professional bodies (such as the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)) regarding the number of patients presenting with ethylene glycol or methanol poisoning, and whether the availability of fomepizole would alter patient management or reduce the use of health sector resource as compared to ethanol in New Zealand. The Committee considered that the priority of its recommendation for fomepizole should be reconsidered in light of the above information if its use would not reduce health sector costs.
- 8.31. Members considered that the reduced monitoring requirements with administration of fomepizole (compared to ethanol which requires regular frequent measurements of metabolic status and ethanol concentration) could mean a preference for its use as a first-line treatment in all patients. Members considered that clinicians may look to initiate treatment with fomepizole on suspicion of poisoning, rather than delaying treatment until diagnosis is confirmed. Members noted that the proposed restriction criteria was generally in line with the TOXINZ indications for treatment with ethanol or fomepizole.
- 8.32. The Committee considered that the dose regimen of fomepizole, including an increased dose after 36 hours, should be a consideration for cost sensitivity analysis.

9. CDK4/6 inhibitors for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer

Applications

- 9.1. The Committee reviewed the following applications:
 - 9.1.1. An application from Pfizer New Zealand Ltd for the use of palbociclib (Ibrance) in combination with an aromatase inhibitor as a first-line treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.
 - 9.1.2. An application from Novartis New Zealand Ltd for the use of ribociclib (Kisqali) in combination with an aromatase inhibitor as a first-line treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.
 - 9.1.3. An application from the Breast Cancer Aotearoa Coalition (BCAC) for the use of palbociclib (Ibrance) in combination with fulvestrant for the second-line treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.
- 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 palbociclib be funded with a **low** priority for use in combination with an aromatase inhibitor as a first-line treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.
- 9.4. The Committee **recommended** that ribociclib be funded with a **low** priority for use in combination with an aromatase inhibitor as a first-line treatment for hormone receptor-positive, HER2 negative locally advanced or metastatic breast cancer.
- 9.5. The Committee **recommended** that palbociclib be funded with **medium** priority for use in combination with fulvestrant as a second-line treatment for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.
- 9.6. The Committee considered that the evidence suggests there is a class effect associated with cyclin dependent kinase 4/6 inhibitors for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer and that these agents be funded subject to the following Special Authority criteria as recommended by the Cancer Treatments Subcommittee:

Special Authority for Subsidy – Retail Pharmacy-Specialist

Initial application (first line) only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has unresectable locally advanced or metastatic breast cancer; and
2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
3. Patient has an ECOG performance score of 0-2; and
4. Patient has not received prior systemic treatment for metastatic disease; and
5. Patient has been amenorrhoeic for 12 months of greater, either naturally or induced, with endocrine levels consistent with a postmenopausal state.
6. Treatment must be used in combination with an endocrine partner.

Initial application (second line) - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has unresectable locally advanced or metastatic breast cancer; and
2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
3. Patient has an ECOG performance score of 0-2; and
4. Patient has relapsed or progressed during prior endocrine therapy; and
5. Treatment must be used in combination with an endocrine partner.

Renewal (first- or second-line) - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Treatment must be used in combination with an endocrine partner; and
2. No evidence of progressive disease; and
3. The treatment remains appropriate and the patient is benefitting from treatment.

Discussion

- 9.7. The Committee considered that advanced breast cancer (aBC) is currently considered incurable, and that the estimated 5-year survival rate is 25%.
- 9.8. The Committee considered that approximately 60% of patients with aBC have HR-positive, HER2-negative disease.
- 9.9. The Committee noted that the application for the use of palbociclib in combination with an aromatase inhibitor (AI) as a first-line treatment for hormone receptor (HR)-positive,

human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (aBC) was considered by the Cancer Treatments Subcommittee's (CaTSoP) in [September 2018](#). The Committee noted that the application for the use of palbociclib in combination with fulvestrant for the second-line treatment for HR-positive, HER2-negative aBC was considered by CaTSoP in April 2019 (publication of minutes pending). The Committee reviewed the relevant record regarding palbociclib from both of these CaTSoP meetings alongside the applications listed above.

- 9.10. The Committee noted and agreed with CaTSoP's view that the standard first- and second-line therapy for patients with HR-positive, HER2-negative aBC is endocrine therapy with either an AI or tamoxifen, and that patients who progress after two lines of endocrine therapy or have visceral disease are likely to receive chemotherapy.
- 9.11. The Committee noted CaTSoP's previous discussion of the number of patients with HR-positive, HER2-negative disease, and considered that the estimates of up to 550 patients eligible for first-line treatment and 400 for second-line treatment were reasonable.
- 9.12. The Committee noted that the cyclin-dependent kinases 4 and 6 (CDK4/6) are fundamental drivers of the cell cycle, and that CDK4/6 inhibitors are thought to act by reducing phosphorylation of the retinoblastoma protein resulting in G1 cell cycle arrest.
- 9.13. The Committee noted that there are currently three CDK4/6 inhibitors in late stage clinical development: palbociclib, ribociclib, and abemaciclib. The Committee noted that palbociclib is currently approved in New Zealand for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer, either in combination with an AI or in combination with fulvestrant in women who have received prior endocrine therapy. The Committee noted that an application for ribociclib is currently being assessed by Medsafe.

Palbociclib – First Line

- 9.14. The Committee noted that in September 2018 CaTSoP recommended that palbociclib be funded with a medium priority for use in combination with an AI as a first-line treatment for HR-positive, HER2-negative locally advanced or metastatic breast cancer ([CaTSoP minutes – September 2018](#)).
- 9.15. The Committee noted that palbociclib is administered orally at a dose of 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days; treatment is continued as long as the patient is deriving clinical benefit or until unacceptable toxicity occurs.
- 9.16. The Committee noted an open-label, Phase 1, dose-escalation trial which investigated the dose-limiting toxicity and maximum tolerated dose of palbociclib in 41 patients with retinoblastoma protein-positive advanced solid tumours ([Flaherty et al. Clin Cancer Res. 2012;18:568-76](#)).
- 9.17. The Committee noted a single-arm, Phase 2 trial which investigated the efficacy of palbociclib in 37 patients with retinoblastoma protein-positive aBC ([DeMichele et al. Clin Cancer Res. 2015;21:995-1001](#)).
- 9.18. The Committee noted the open-label, randomised, Phase 2 PALOMA-1 trial which investigated the safety and efficacy of palbociclib in combination with letrozole compared with letrozole alone for the first-line treatment of 165 postmenopausal women with oestrogen receptor-positive, HER2-negative aBC ([Finn et al. Lancet Oncol. 2015;16:25-35](#)). The Committee noted that the progression-free survival (PFS) was 20.2 months in the palbociclib plus letrozole group compared with 10.2 months in the letrozole monotherapy group (HR 0.488; 95% CI 0.319 to 0.748; one-sided $P=0.0004$). The Committee noted that the median overall survival (OS) was 37.5 months in the palbociclib plus letrozole group compared with 33.3 months in the letrozole group (HR

0.813; 95% CI 0.492 to 1.345; two-sided $P=0.42$). The Committee noted that the most common grade 3/4 adverse events (AEs) were neutropenia (54% palbociclib plus letrozole vs 1% letrozole) and leukopenia (19% palbociclib plus letrozole vs 0% letrozole).

- 9.19. The Committee noted the publication of the pain analysis from the PALOMA-1 trial which reported that there was no significant difference in Pain Severity or Pain Interference scores of the Brief Pain Inventory between patients receiving palbociclib plus letrozole compared with letrozole alone ([Bell et al. Curr Med Res Opin. 2016;32:956-65](#)).
- 9.20. The Committee noted the double-blind, randomized, placebo-controlled, Phase 3 PALOMA-2 trial which investigated the efficacy and safety of palbociclib plus letrozole compared with placebo plus letrozole for the first-line treatment of 666 postmenopausal women with oestrogen receptor-positive, HER2-negative aBC ([Finn et al. N Engl J Med. 2016;375:1925-36](#)). The Committee noted that after a median follow-up of 23 months, the PFS was 24.8 months in the palbociclib plus letrozole arm compared with 14.5 months in the placebo plus letrozole arm (HR 0.58; 95% CI 0.46 to 0.72; $P<0.001$). The Committee noted that OS data were immature at the time of this analysis. The Committee noted that the incidence of grade 3/4 AEs was substantially higher in patients who received palbociclib plus letrozole compared with those who received placebo plus letrozole (76% palbociclib plus letrozole vs 24% placebo plus letrozole).
- 9.21. The Committee noted the publication of the quality of life (QoL) analysis from the PALOMA-2 trial ([Rugo et al. Ann Oncol. 2018;29:888-894](#)). The Committee noted that after a median follow-up of 23 months there were no significant between-arm differences in change from baseline in Functional Assessment of Cancer Therapy (FACT)-breast Total, FACT-general Total, or EuroQoL-5D scores. The Committee noted that an improvement in pain scores was observed in the palbociclib plus letrozole compared with the placebo plus letrozole arm (-0.256 vs -0.098; $P=0.018$). The Committee noted that deterioration in QoL was delayed in patients without progression compared with those with progression, and in patients with partial or complete response compared to those who did not respond.
- 9.22. The Committee noted the publication of an extended follow-up of the PALOMA-2 trial ([Rugo et al. Breast Cancer Res Treat. 2019;174:719-29](#)). The Committee noted that after a median follow-up of approximately 38 months, the median PFS was 27.6 months in the palbociclib plus letrozole group compared with 14.5 months in the placebo plus letrozole group (HR 0.563; one-sided $P<0.0001$). The Committee noted that the use of chemotherapy was delayed in patients who received palbociclib plus letrozole compared with those receiving placebo plus letrozole (40.4 months vs 29.9 months) and QoL was maintained.
- 9.23. The Committee agreed with CaTSoP's conclusion that there was reasonable evidence of a modest effect from the use of palbociclib in combination with a non-steroidal AI as a first-line treatment for postmenopausal women with HR-positive HER2-negative aBC.

Ribociclib – First Line

- 9.24. The Committee noted that ribociclib is administered orally at a dose of 600 mg (three 200 mg tablets) once daily for 21 consecutive days followed by 7 days off treatment; treatment is continued until disease progression or unacceptable toxicity occurs.
- 9.25. The Committee noted a first-in-human Phase 1 trial which investigated the maximum-tolerated dose, the recommended dose for expansion, safety, and preliminary pharmacokinetics and pharmacodynamics of ribociclib in patients with retinoblastoma protein-positive advanced solid tumours or lymphoma ([Infante et al. Clin Cancer Res. 2016;22:5696-705](#)).

- 9.26. The Committee noted a Phase 1b trial which investigated the safety, efficacy, and pharmacokinetics of ribociclib in postmenopausal women with oestrogen receptor-positive, HER2-negative aBC ([Juric et al. J Clin Oncol. 2016;34\[15 suppl\]:568-568](#)).
- 9.27. The Committee noted the Phase 3 MONALEESA-2 trial which investigated the efficacy and safety of ribociclib plus letrozole compared with placebo plus letrozole for the first-line treatment of 668 postmenopausal women with HR-positive, HER2-negative aBC ([Hortobagyi et al. Ann Oncol. 2018;29:1541-7](#)). The Committee noted that after a median follow-up of 26.4 months, the median PFS was 25.3 months in the ribociclib plus letrozole group compared with 16.0 month in the placebo plus letrozole group (HR 0.568; 95% CI 0.457 to 0.704; log-rank $P=9.63 \times 10^{-8}$). The Committee noted that the most common grade 3/4 AEs were neutropenia (62% in the ribociclib group vs 1.2% in the placebo group) and leukopenia (21% vs 0.9%).
- 9.28. The Committee noted the Phase 3 MONALEESA-7 trial which investigated the efficacy and safety of ribociclib plus endocrine therapy (tamoxifen or an AI, with goserelin) compared with placebo plus endocrine therapy in 672 premenopausal women with HR-positive, HER2-negative aBC who had not previously received a CDK4/6 inhibitor ([Tripathy et al. Lancet Oncol. 2018;19:904-15](#)). The Committee noted that after a median follow-up of 19.2 months, the median PFS was 23.8 months in the ribociclib plus endocrine therapy group compared with 13.0 months in the placebo plus endocrine therapy group (HR 0.55; 95% CI 0.44 to 0.69; $P<0.0001$). The Committee noted that the most common grade 3/4 AEs were neutropenia (61% ribociclib plus endocrine therapy vs 4% placebo plus endocrine therapy) and leukopenia (14% vs 1%).
- 9.29. The Committee noted the Phase 3 MONALEESA-3 trial which investigated the efficacy and safety of ribociclib plus fulvestrant compared with placebo plus fulvestrant in 484 postmenopausal women with HR-positive, HER2-negative aBC who were treatment naïve or had received up to one line of prior endocrine therapy in the advanced setting ([Slamon et al. J Clin Oncol. 2018;36:2465-72](#)). The Committee noted that after a median follow-up of 20.4 months, the median PFS was 20.5 months in the ribociclib plus fulvestrant group compared with 12.8 months in the placebo plus fulvestrant group (HR 0.593; 95% CI 0.480 to 0.732; $P<0.001$). The Committee noted that the most common grade 3/4 AEs were neutropenia (53% ribociclib plus fulvestrant vs 0% placebo plus fulvestrant) and leukopenia (14% vs 0%).

Palbociclib – Second Line

- 9.30. The Committee noted that in April 2019 CaTSoP recommended that palbociclib in combination with fulvestrant for the second-line treatment of HR-positive, HER2-negative aBC be funded with a medium priority (publication of minutes pending).
- 9.31. The Committee noted that the primary evidence for the use of palbociclib for the second-line treatment of aBC is provided by the double-blind, randomised, placebo-controlled, Phase 3 PALOMA-3 trial which investigated the efficacy of palbociclib plus fulvestrant compared with placebo plus fulvestrant in 521 women of any menopausal status with HR-positive, HER2-negative aBC who had relapsed or progressed during prior endocrine therapy. The Committee considered evidence from the following publications:
- P PALOMA-3 interim analysis, median follow-up 5.6 months ([Turner et al. N Engl J Med. 2015;373:209-19](#)).
 - PALOMA-3 final analysis, median follow-up 8.9 months ([Cristofanilli et al. Lancet Oncol. 2016;17:425-39](#)).
 - PALOMA-3 detailed safety analysis, median follow-up 8.9 months ([Verma et al. Oncologist. 2016;21:1165-75](#)).
 - PALOMA-3 overall survival analysis, median follow-up 44.8 months ([Turner et al. N Engl J Med. 2018;379:1926-36](#)).

- PALOMA-3 patient reported outcomes ([Harbeck et al. Ann Oncol. 2016;27:1047-54](#)).
- 9.32. The Committee noted that at the time of the final analysis of PALOMA-3 (median follow-up 8.9 months), Cristofanilli et al. 2016 reported a median PFS of 9.5 months in the palbociclib plus fulvestrant group compared with 4.6 months in the placebo plus fulvestrant group (HR 0.46; 95% CI 0.36 to 0.59; $P<0.0001$). The Committee noted that the most common grade 3/4 AEs were neutropenia (65% palbociclib plus fulvestrant vs 1% placebo plus fulvestrant), anaemia (3% vs 2%), and leukopenia (28% vs 1%).
- 9.33. The Committee noted that at the time of the prespecified OS analysis of PALOMA-3 (median follow up 44.8 months), Turner et al. 2018 reported a median OS of 34.9 months in the palbociclib plus fulvestrant group compared with 28.0 months in the placebo plus fulvestrant group (stratified HR 0.81; 95% CI 0.64 to 1.03; $P=0.09$). The Committee noted that while this was not a statistically significant difference, the OS did favour treatment with palbociclib plus fulvestrant (difference in OS of 6.9 months).
- 9.34. The Committee noted the QoL analysis from the PALOMA-3 trial, in which Harbeck et al. 2016 reported that the estimated overall global QoL scores favoured the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group (66.1 vs 63.0; $P=0.0313$). The Committee noted there was also an improvement in pain from baseline in the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group (-3.3 vs 2.0; $P=0.0011$). The Committee noted there were no between-arm differences in breast-cancer specific quality of life functional domains or breast or arm symptoms as measured using the EORTC QLQ-BR23 instrument; and that there was a delay in deterioration in global QoL in the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group.
- 9.35. The Committee agreed with CaTSoP's conclusion that there is a significant health need for women with previously treated HR-positive, HER2-negative aBC, and that PALOMA-3 provides good quality evidence that palbociclib in combination with fulvestrant provides a clinically meaningful PFS benefit in this setting.

General

- 9.36. The Committee noted the findings of three meta-analyses which investigated the benefits and risks associated with the use of CDK4/6 inhibitors for the treatment of HR-positive, HER2-negative aBC ([Messina et al. Breast Cancer Res Treat. 2018;172:9-21](#); [Guo et al. Target Oncol. 2019;14:139-48](#); [Petrelli et al. Breast Cancer Res Treat. 2019;174:597-604](#)). The Committee considered that these meta-analyses, in addition to the Committee's review of the primary clinical trials of palbociclib and ribociclib, indicate that there is a class effect with the CDK4/6 inhibitors, and that the agents within this class can be considered to provide the same or similar therapeutic effect.
- 9.37. The Committee noted that in April 2019, CaTSoP reviewed the evidence available to date for the use of palbociclib, ribociclib, and abemaciclib for the treatment of aBC (publication of minutes pending). The Committee noted that based on this CaTSoP considered there is a class effect with CDK4/6 inhibitors, and that there is likely to be no significant difference in which endocrine partner the CDK4/6 inhibitors are combined with.
- 9.38. The Committee noted that there is no data available at this time regarding switching between CDK4/6 inhibitors or continuing the same CDK4/6 inhibitor but switching the endocrine partner at progression. The Committee noted that the PACE trial (NCT03147287) and the TRINITI trial (NCT02732119) which are investigating the use of CDK4/6 inhibitors following prior CDK4/6 inhibitor treatment are currently underway.
- 9.39. The Committee noted that there are a large number of trials underway investigating CDK4/6 inhibitors in breast cancer, including in different breast cancer subtypes, as

different treatment combinations, and for the treatment of different stages of breast cancer.

- 9.40. The Committee noted that there are a number of pharmacoeconomic analyses published regarding the cost effectiveness of CDK4/6 inhibitors for the treatment of breast cancer ([Gogate et al. Breast Cancer Res Treat. 2019;174:343-55](#); [Zhang B. Breast Cancer Res Treat. 2019;175:775-779](#); [Mamiya et al. Ann Oncol. 2017;28:1825-31](#)). The Committee noted that these studies generally concluded that CDK4/6 inhibitors exceed willingness to pay thresholds at the prices currently being offered. The Committee noted that the pharmacoeconomic analyses that compared the cost effectiveness of ribociclib to palbociclib found that ribociclib was a cost-effective alternative to palbociclib, noting that these analyses are largely driven by the price offered in the country they were conducted in ([Mistry et al. J Manag Care Spec Pharm. 2018;24:514-23](#); [Galve-Calvo et al. Clinicoecon and Outcomes Research 2018;10:773-90](#)).
- 9.41. The Committee noted that the prices currently being sought by the suppliers of CDK4/6 inhibitors in New Zealand are high, which adversely effects the cost effectiveness of these agents.
- 9.42. The Committee considered that no biomarker has yet been identified that predicts sensitivity to CDK4/6 inhibitors, but that there is some indication that patients with oestrogen receptor-positive disease may receive the most benefit.
- 9.43. The Committee noted CaTSoP's suggestion at its April 2019 meeting that patients with hormone-sensitive disease may benefit the most from treatment with a CDK4/6 inhibitor, but considered that the analyses conducted by Messina et al. 2018 indicated that both endocrine-sensitive and endocrine resistant patients benefit from treatment with a CDK4/6 inhibitor plus endocrine therapy ([Messina et al. Breast Cancer Res Treat. 2018;172:9-21](#)).
- 9.44. The Committee considered there is limited evidence available at this time to definitively demonstrate which endocrine partner should be used in combination with a CDK4/6 inhibitor. The Committee considered that the majority of the evidence regarding first-line treatment indicates that an AI is the most appropriate endocrine partner in this setting. The Committee considered that the majority of the data available regarding second-line treatment has been conducted in combination with fulvestrant, but considered that the evidence for the use of CDK4/6 inhibitors was relatively early in its development and the Committee could support the use of CDK4/6 inhibitors in combination with other endocrine partners if evidence supporting this became available.
- 9.45. The Committee noted that there is an increased frequency of grade 3/4 neutropenia and leukopenia with CDK4/6 inhibitor treatment, but that this does not appear to affect QoL ([Rugo et al. Ann Oncol. 2018;29:888-94](#)). The Committee noted that if a CDK4/6 inhibitor were funded, there may be an increased requirement for the investigation and treatment of neutropenia and so additional associated costs to the sector from this.
- 9.46. The Committee noted that there are limited OS data currently available for the use of first line CDK4/6 inhibitors, and the OS data available to date for second line use of CDK4/6 inhibitors has not shown a statistically significant difference compared with placebo. The Committee noted CaTSoP's April 2019 discussion of the difficulties in assessing OS in disease such as HR-positive HER2-negative breast cancer where patients have long survival times and receive multiple lines of treatment (CaTSoP April 2019 - publication of minutes pending).
- 9.47. The Committee noted that palbociclib plus fulvestrant for the second-line treatment of HR-positive, HER2-negative aBC has a score of 4 on the ESMO-Magnitude of Clinical Benefit Scale; palbociclib or ribociclib in combination with letrozole for the first-line treatment of HR-positive, HER2-negative aBC have scores of 3 on the ESMO-Magnitude of Clinical Benefit Scale.

- 9.48. The Committee considered that there is moderate quality evidence that palbociclib or ribociclib used in combination with an endocrine partner as a first-line treatment provides a modest improvement in PFS and maintains QoL in patients with HR-positive, HER2-negative aBC. The Committee considered that while there are good quality Phase 3 randomized controlled trials available, that the interpretation of results is limited by the emphasis placed on PFS. The Committee considered that a composite analysis of PFS, OS, safety, and QoL data would strengthen the evidence base.
- 9.49. The Committee considered that there is good quality evidence that palbociclib in combination with fulvestrant as a second-line treatment provides a modest improvement in PFS with maintenance of QoL in patients with HR-positive, HER2-negative aBC.
- 9.50. The Committee considered that it was uncertain whether the use of a CDK4/6 in a first or second-line setting would provide greater overall benefit for patients, as there was a lack of evidence to inform whether these agents altered tumour biology and/or the efficacy of subsequent treatments. The Committee considered it was likely that the use of a CDK4/6 inhibitor would alter prescriber behaviour for later line treatments.
- 9.51. The Committee considered that patients who have already progressed following one line of endocrine therapy have a higher health need than those who are treatment naïve due to a lack of alternative treatment options.
- 9.52. The Committee considered that the Special Authority criteria previously recommended by CaTSoP for the first- and second-line use of CDK4/6 inhibitors are appropriate.

10. Everolimus for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer

Application

- 10.1. The Committee reviewed the application from the Breast Cancer Aotearoa Coalition (BCAC) for the use of everolimus in the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer.
- 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 everolimus for the treatment of HR-positive, HER2-negative, advanced breast cancer be **declined** noting the poor quality of evidence to support its use and a lack of demonstrated benefit in the mature evidence for either progression-free survival (PFS) or overall survival (OS).

Discussion

- 10.4. The Committee noted that the application from the Breast Cancer Aotearoa Coalition (BCAC) requests funding for everolimus for treatment of HR-positive, HER2-negative, advanced breast cancer (aBC) in post-menopausal women after recurrence or progression following treatment with a non-steroidal aromatase inhibitor (AI).
- 10.5. The Committee noted that the health need, epidemiology and the current New Zealand treatment paradigm for the treatment of patients with HR-positive, HER2-negative, aBC have been well documented in recent records of CaTSoP and PTAC meetings regarding the CDK4/6 inhibitors, palbociclib and ribociclib (including the record of this PTAC meeting).
- 10.6. The Committee considered that, if funded, everolimus would likely be placed in the New Zealand treatment paradigm alongside the CDK4/6 inhibitors as another second-line option for this indication.

- 10.7. The Committee noted that everolimus is a protein kinase inhibitor which targets and inhibits mTORC1, a kinase which is critical to many cellular processes and which is dysregulated in most human cancers. The Committee noted that mTOR is one of several interconnected cellular pathways and that inhibition of one pathway can cause upregulation of another pathway, therefore the Committee considered that it was important for any treatment which inhibits one or more of these pathways to be supported by sound evidence of efficacy and safety.
- 10.8. The Committee noted that everolimus is not Medsafe-approved for the treatment of aBC, however, it is registered by Medsafe for the treatment of neuroendocrine tumours, renal cell carcinoma and subependymal giant cell astrocytoma. The Committee noted that everolimus is administered as a 10 mg oral once daily dose.
- 10.9. The Committee noted that the applicant has requested funding for everolimus in combination with exemestane or tamoxifen (both of which are Medsafe-registered and currently funded without restriction) or with fulvestrant (which is not Medsafe-registered and is not currently funded for use in any setting).

Everolimus with exemestane

- 10.10. The Committee noted the key evidence for everolimus in combination with exemestane comes from the randomised, phase III, BOLERO-2 trial which investigated everolimus with exemestane compared to exemestane with placebo in 724 post-menopausal patients with HR-positive, HER2-negative aBC who had recurrence or progression while receiving previous treatment with a nonsteroidal AI ([Baselga et al, N Engl J Med. 2012;366:520-9](#)). The Committee noted that 77% of BOLERO-2 patients had bone lesions, 59% of patients had visceral disease, 26% of patients received previous chemotherapy and 20% of patients had received no previous therapy for metastatic breast cancer.
- 10.11. The Committee noted the results of the interim analysis of progression-free survival (PFS) in BOLERO-2, which report investigator-assessed median PFS of 6.9 months with everolimus and exemestane compared to 2.8 months with placebo and exemestane (HR 0.43, 95% CI: 0.35 to 0.54, $P < 0.001$) ([Baselga et al, N Engl J Med. 2012;366:520-9](#)).
- 10.12. The Committee noted the results from the final analysis of PFS of the BOLERO-2 trial which report median PFS of 7.8 months with everolimus and exemestane compared to 3.2 months with placebo and exemestane (HR 0.45, 95% CI: 0.38 to 0.54, $P < 0.001$) ([Yardley et al. Adv Ther. 2013;30:870-84](#)).
- 10.13. The Committee noted the results from the subgroup analysis of BOLERO-2 trial patients according to visceral involvement status, which report median PFS of 6.8 months with everolimus and exemestane compared to 2.8 months with placebo and exemestane in patients with visceral involvement compared to PFS of 9.9 months and 4.2 months respectively for patients without visceral involvement ([Campone et al. Eur J Cancer. 2013;49:2621-32](#)). The Committee considered that the reduced benefit observed for patients with visceral involvement aligned with the poorer prognosis of this patient group as compared to patients without visceral disease.
- 10.14. The Committee noted the results from the subgroup analysis of elderly BOLERO-2 trial patients which report median PFS of 6.8 months with everolimus and exemestane compared to 1.5 months with placebo and exemestane, in patients ages 70 years and over ([Pritchard et al. Clin Breast Cancer. 2013;13:421-32.e8](#)). The Committee considered that the results in this elderly subgroup were consistent with other populations.
- 10.15. The Committee noted the results from the final analysis of overall survival (OS) in BOLERO-2 trial patients, which report median OS of 31.0 months with everolimus and exemestane compared to 26.6 months with placebo and exemestane (HR 0.89, 95% CI

- 0.73 to 1.10, $P = 0.1426$) ([Piccart et al. Ann Oncol. 2014;25:2357-62](#)). The Committee considered that even after a reasonably long follow-up duration and with adequate patient numbers contributing to data beyond 3 years, the study was inadequately powered to confirm the reported OS difference and the reported OS results were not statistically significant.
- 10.16. The Committee noted the results of post-progression survival (PPS) of 492 BOLERO-2 trial patients who had progressed at the time of the final PFS analysis, which report median PPS of 20.8 months with everolimus and exemestane compared to 19.3 months with placebo and exemestane ([Piccart et al. Ann Oncol. 2014;25:2357-62](#)). The Committee considered the PPS results to be similar in each arm and no survival benefit was demonstrated.
- 10.17. The Committee noted that BOLERO-2 trial patients who received placebo with exemestane were more likely to receive chemotherapy (63%) than patients who received everolimus and exemestane (53%) ([Piccart et al. Ann Oncol. 2014;25:2357-62](#)). The Committee considered that the results reported by Piccart et al. suggest that whether or not a patient received post-trial chemotherapy had no impact on PPS, however, the time to first chemotherapy was longer with everolimus and exemestane (11.9 months) compared to with placebo and exemestane (6.0 months). The Committee considered that investigators may be able to determine which patients were receiving everolimus by the incidence of stomatitis, and consequently that patients thought to be receiving placebo would receive more aggressive therapy.
- 10.18. The Committee noted the results of an analysis of adverse event (AE) data from the BOLERO-2 trial, which report that 67% of patients who received everolimus and exemestane required dose interruptions or reductions compared to 24% with placebo and exemestane ([Rugo et al. Ann Oncol. 2014;25:808-15](#)). The Committee noted that two thirds of patients receiving everolimus developed stomatitis and that a large proportion of patients discontinued treatment due to this AE. The Committee noted that 8 patients who received everolimus and exemestane died due to AEs compared to 1 AE-related death with placebo and exemestane; and considered the combination of everolimus and exemestane to have a significant toxicity profile.
- 10.19. The Committee noted the results of the BOLERO-2 trial analysis of treatment effects on health-related Quality of Life (QoL), which report a median time to definitive deterioration (TDD) in QoL of 8.3 months with everolimus and exemestane compared to 5.8 months with placebo and exemestane (HR 0.74, $P = 0.0084$) ([Burriss et al. Cancer. 2013;119:1908-15](#)). The Committee noted that, at the 10-point minimal clinically important difference, the median TDD was 11.7 months for everolimus and exemestane compared to 8.4 months for placebo and exemestane, although this result was not statistically significant (HR 0.80; $P = .10$). The Committee considered the slower deterioration in QoL in patients who received everolimus and exemestane potentially could be attributed to delayed disease progression.
- 10.20. The Committee noted the results from the correlative analysis investigating genetic alterations and everolimus benefit in BOLERO-2 trial patients, which report that PFS with everolimus was generally the same regardless of alteration status (eg PIK3CA, FGFR1, or CCND1 alterations), although patients with chromosomal instability may receive more PFS benefit than those without ([Hortobagyi et al. J Clin Oncol. 2016;34:419-26](#)). The Committee considered that there was currently insufficient evidence that genetic markers were predictive of which patients would receive better outcomes from treatment with everolimus.
- 10.21. The Committee noted the results of the open-label, randomised, phase II, three-arm BOLERO-6 trial investigating everolimus with exemestane compared to everolimus alone compared to capecitabine alone, in 309 post-menopausal women with oestrogen receptor-positive (ER-positive), HER2-negative breast cancer ([Jerusalem et al. JAMA Oncol. 2018;4:1367-74](#)). The Committee noted that the authors report median OS of

23.1 months with everolimus plus exemestane compared to 29.3 months with everolimus alone (HR 1.27, 90% CI: 0.95 to 1.70) compared to 25.6 months with capecitabine (HR 1.33, 90% CI: 0.99 to 1.79). The Committee considered that the trial results suggest that there is little difference in benefit from the three treatment arms, although the reported confidence intervals are wide, and the survival curves suggest capecitabine has the greatest benefit.

Everolimus with tamoxifen

10.22. The Committee noted the results of the randomised, open-label, phase II TAMRAD trial which investigated everolimus with tamoxifen compared to tamoxifen alone in 111 women with HR-positive, HER2-negative metastatic breast cancer with prior exposure to aromatase inhibitors ([Bachelot et al. J Clin Oncol. 2012;30:2718-24](#)). The Committee noted the authors report median PFS of 8.6 months with everolimus and tamoxifen compared to 4.5 months with tamoxifen alone, and that the risk of death was 55% lower in patients who received everolimus plus tamoxifen compared to tamoxifen alone (HR, 0.45, 95% CI: 0.24 to 0.81).

10.23. The Committee noted that Bachelot et al. reported a higher incidence of AEs in patients who received everolimus with tamoxifen compared to those who received tamoxifen alone and considered that the increased toxicity was predominantly due to everolimus. The Committee considered that, although the number of patients in the TAMRAD trial was small, the results were similar to the BOLERO-2 trial results.

Everolimus with fulvestrant

10.24. The Committee noted the results of the randomised, double-blind, phase II, PrE0102 trial which investigated everolimus with fulvestrant compared to placebo with fulvestrant in 131 post-menopausal women with ER-positive, HER2-negative aBC (Kornblum et al. J Clin Oncol. 2018;36:1556-63). The Committee noted that the authors report median PFS of 5.1 months with placebo and fulvestrant compared to 10.3 months with everolimus and fulvestrant (HR 0.61, 95% CI: 0.40 to 0.92, P = .02), and median OS of 28.3 months with everolimus and fulvestrant compared to 31.4 months with placebo and fulvestrant, although the OS result did not reach statistical significance (HR 1.31, 95% CI: 0.72 to 2.38, P = .37). The Committee considered that these results suggest a benefit of everolimus with fulvestrant in terms of PFS but no OS benefit from this treatment combination.

Other evidence

10.25. The Committee noted the results of the open-label, single-arm, phase II BOLERO-4 trial which investigated everolimus with letrozole for the first-line treatment of 202 women with oestrogen receptor-positive, HER2-negative aBC ([Royce et al. JAMA Oncol. 2018;4:977-84](#)). The Committee noted that the authors report median PFS was 22.0 months (95% CI: 18.1 to 25.1 months) with everolimus and letrozole, but median OS was not reached. The Committee considered that the BOLERO-4 results suggest much longer PFS compared to BOLERO-2, specifically, that survival of BOLERO-4 patients was about 70% at 3 years compared to survival of BOLERO-2 patients of about 40% at 3 years, however the Committee considered it likely this could be due to differences between the two trial patient populations.

10.26. The Committee also noted the following evidence provided by the applicant:

- [Noguchi et al. Breast Cancer. 2014;21:703-14.](#)
- [Beck et al. Breast Cancer Res Treat. 2014;143:459-67.](#)
- [Ciruelos et al. Clin Transl Oncol. 2018;20:753-60.](#)
- [Cazzaniga et al. Breast. 2017;35:115-21.](#)
- [Tesch et al. Int J Cancer. 2019;144:877-85.](#)

- [Ciccarese et al. Breast Cancer Res Treat. 2017;163:587-94.](#)
- [Moscetti et al. Breast. 2016;29:96-101.](#)
- [Chocteau-Bouju et al. Breast. 2015;24:718-22.](#)
- [Gong et al. Oncotarget. 2017;8:59810-22.](#)
- [Pouget et al. Oncology. 2015;89:319-31.](#)
- [Vargo et al. Support Care Cancer. 2016;24:2913-8.](#)
- [Bajpai et al. Indian J Cancer. 2016;53:464-7.](#)
- [Wheler et al. Oncotarget. 2014;5:3029-38.](#)
- [Safra et al. Clin Breast Cancer. 2018;18:e197-e203.](#)

General

10.27. The Committee considered that there was mature evidence for everolimus in the treatment of the requested population but that overall, neither a clinically important OS or PFS benefit was demonstrated. The Committee considered that there were significant limitations in the available evidence, which was of poor quality (ESMO grade 2). The Committee considered that there was uncertainty regarding the appropriate dose of everolimus and concerns about AEs.

10.28. The Committee noted that a large trial of everolimus compared with a range of aromatase inhibitors (including anastrozole, exemestane and letrozole) is ongoing, however, the Committee considered that any role for everolimus in the treatment paradigm for aBC remained unclear (particularly noting the number of treatments for breast cancer in late stage development and being brought to market internationally, both as monotherapies and in combination regimens).

11. Nab-paclitaxel for the treatment of metastatic breast cancer

Application

- 11.1. The Committee reviewed additional information submitted by the Breast Cancer Aotearoa Coalition (BCAC) to support the funding of nab-paclitaxel for the treatment of all patients with metastatic breast cancer (mBC).
- 11.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 11.3. The Committee considered that the updated evidence for nab-paclitaxel for the treatment of mBC did not support a change in the recommendation for funding, and reiterated its previous recommendation that nab-paclitaxel for the treatment of metastatic breast cancer be listed only if cost-neutral to weekly paclitaxel, taking into account pharmaceutical and administration costs.

Discussion

- 11.4. The Committee noted that the application from the Breast Cancer Aotearoa Coalition (BCAC) requests funding for nab-paclitaxel for the treatment of metastatic breast cancer (mBC). The Committee noted that nab-paclitaxel is registered by Medsafe for three indications, of which one is for mBC for treatment after failure of anthracycline therapy.
- 11.5. The Committee noted that applications for nab-paclitaxel for the treatment of mBC had been previously considered from Specialised Therapeutics Limited in 2010 and from the New Zealand Breast Cancer Special Interest Group (NZBSIG) in 2013, and that funding

for nab-paclitaxel had previously been recommended only if cost-neutral to weekly paclitaxel, taking into account pharmaceutical and administration costs.

- 11.6. The Committee noted that the health need, epidemiology and New Zealand treatment paradigm for patients with mBC has been well documented in previous committee minutes regarding review of applications for nab-paclitaxel for the treatment of mBC.
- 11.7. The Committee noted that the following evidence provided in this application had been reviewed previously:
- [Gradishar et al. J Clin Onc 2009;27:3611-9](#)
 - [Guan et al. J Clin Onc 2007;25\(18 Suppl\):1038](#) (abstract supplied; full paper also reviewed: [Guan et al. Asian Pacific J Clin Oncol 2009;5:165-74](#))
 - [Gradishar J Clin Onc 2005;23:7794](#)
 - [Rugo et al. J Clin Onc 2012;30\(18 Suppl\):1002](#)
- 11.8. The Committee noted the updated overall survival (OS) data from the phase II trial of various dose schedules of nab-paclitaxel compared to 3-weekly docetaxel in patients with mBC, which demonstrated a median OS of 33.8 months with weekly nab-paclitaxel (at a dose of 150 mg per square metre) compared to 26.6 months with docetaxel 3-weekly (HR 0.69, no confidence interval provided) ([Gradishar et al. Clinical Breast Cancer 2012;12:313-21](#)). The Committee considered that this evidence supported the previous conclusion of a benefit of the weekly regimen compared to 3-weekly docetaxel.
- 11.9. The Committee noted evidence from a combined analysis of two of the Gradishar papers in patients with mBC aged 65 years and older ([Aapro et al. Breast 2011;20:468-74](#)). The Committee considered this publication to be of limited value as it included only a restricted population of over 65 years, and no analysis was specified nor was a combined relative effect against comparator treatments given.
- 11.10. The Committee noted the subsequent publication of results from the randomised, phase III, three-arm trial of weekly nab-paclitaxel compared to weekly paclitaxel (compared to ixabepilone) for patients with mBC ([Rugo et al. J Clin Oncol 2015;33:2361-9](#)) and the abstract of final OS results from the same study ([Rugo et al. Cancer Res 2018;78\(4 Suppl\):Abstract nr GS3-06](#)). The Committee noted participants had ECOG grade 0 to 1 and considered that, while trial treatment included bevacizumab in both arms, the effect of nab-paclitaxel and paclitaxel could be compared. The Committee noted that quality of life (QoL) data was collected but appeared not to be published.
- 11.11. The Committee noted that [Rugo et al. \(J Clin Oncol 2015;33:2361-9\)](#) reported median progression-free survival (PFS) of 9.3 months with nab-paclitaxel compared to 11 months with paclitaxel (HR 1.2; 95% CI: 1.0 to 1.45), and median OS of 23.5 months with nab-paclitaxel compared to 26.5 months with paclitaxel (HR 1.17, 95% CI: 0.92 to 1.47) although this result was not statistically significant. The Committee noted there was a higher incidence of neuropathy in patients who received nab-paclitaxel (27%) compared to paclitaxel (18%) and that haematologic adverse effects were worse with nab-paclitaxel (55% with grade 3 or higher) compared to paclitaxel (22% with grade 3 or higher).
- 11.12. The Committee noted that the final OS results from [Rugo et al. \(Cancer Res 2018;78\(4 Suppl\):Abstract nr GS3-06\)](#) report median OS of 24.2 months with nab-paclitaxel compared to 27.1 months with paclitaxel (HR 1.10, 95% CI: 0.91 to 1.34) after long-term follow up.
- 11.13. The Committee noted the results of a systematic review of weekly compared to 3-weekly taxane regimens in advanced breast cancer ([Mauri et al. Cancer Treat Rev. 2010;36:69-74](#)) and the results of a meta-analysis of randomised controlled trials using nab-

paclitaxel ([Liu et al. Oncotarget 2017;8:72950-8](#)). The Committee noted that data for each individual trial had previously been reviewed. The Committee considered that the results of the systematic review and meta-analysis of nab-paclitaxel compared to paclitaxel supported the use of weekly therapy, showed no difference in OS (hazard ratio 1.06), reported increased sensory neuropathy in patients who received nab-paclitaxel, and did not provide QoL data.

- 11.14. The Committee discussed hypersensitivity reactions reported in patients receiving paclitaxel. Members noted that hypersensitivity reactions to paclitaxel appeared to be a rare occurrence however some could be severe. The Committee noted that CaTSoP had previously stated that, as it was difficult to determine if hypersensitivity reactions were due to the paclitaxel molecule itself or solvent components of the infusion, this risk is managed by avoiding further treatment with paclitaxel or nab-paclitaxel in patients who have had hypersensitivity reactions to paclitaxel ([CaTSoP minutes March 2014](#)).
- 11.17. The Committee noted that the applicant suggests there is less need for associated medications (eg antihistamines and corticosteroids) with nab-paclitaxel, however, the Committee noted that CaTSoP has previously noted that premedication was not routinely administered to patients receiving weekly paclitaxel because the lower dose was less commonly associated with hypersensitivity reactions, and therefore the weekly administration was the preferred regimen for this agent ([CaTSoP minutes September 2013](#)).
- 11.18. The Committee noted that the above differed to what was detailed in trial evidence and the Medsafe Datasheet, and considered that clarification should be sought from CaTSoP as to whether weekly paclitaxel without premedication remained standard practice in New Zealand and whether patients with a previous hypersensitivity reaction to paclitaxel would be re-challenged with nab-paclitaxel, if available.
- 11.19. The Committee considered that the updated evidence for nab-paclitaxel for the treatment of mBC did not support a change in the recommendation for funding of this agent over currently funded paclitaxel unless pricing was cost-neutral or better for the health sector. The Committee considered currently available evidence did not show a clinical benefit based on OS or QoL and reported more adverse events with nab-paclitaxel.

12. Prucalopride for chronic slow-transit constipation

Application

- 12.1. The Committee reviewed a funding application from a clinician with the backing of the New Zealand Society of Gastroenterology for prucalopride (Resotrans) for the treatment of adults with chronic slow-transit constipation in whom regular laxatives have failed to provide adequate relief.
- 12.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 12.3. The Committee recommended that the application for prucalopride for the treatment of chronic slow-transit constipation be **deferred** pending advice from the Gastroenterology Subcommittee regarding how to define the population with the highest need and those mostly likely to benefit, and the evidence for the use of prucalopride in this population.

Discussion

- 12.4. The Committee noted that the application for prucalopride for the treatment of chronic slow-transit constipation was reviewed by the Gastroenterology Subcommittee in [October 2018](#). At this time, the Subcommittee considered that the evidence available demonstrated that prucalopride provided a modest but clinically significant benefit for

patients with severe chronic constipation and recommended that prucalopride be funded with a medium priority. The Committee reviewed these minutes in [February 2019](#) and considered that the population described by the proposed Special Authority criteria was potentially very large, and that the evidence reviewed suggested only a modest effect. The Committee considered the funding of prucalopride represented a significant fiscal risk and requested that the Committee have the opportunity to review the full application.

- 12.5. The Committee noted that prucalopride is a selective, high-affinity serotonin receptor agonist which facilitates cholinergic and excitatory noradrenergic, non-cholinergic neurotransmission resulting in the initiation of high amplitude propagated contractions in the colon, colonic propulsion, right colonic emptying, and gastric emptying via small bowel transit.
- 12.6. The Committee noted that prucalopride is approved by Medsafe for the treatment of chronic constipation in adults in whom laxatives have failed to provide adequate relief.
- 12.7. The Committee noted that prucalopride is provided as a 1 mg or 2 mg film-coated tablet and is administered at a dose of 2 mg once daily for adults. The Committee noted that prucalopride is not recommended for use in children and adolescents younger than 18 years of age.
- 12.8. The Committee noted that there are three major subtypes of chronic idiopathic constipation: normal transit (functional constipation), rectal evacuation disorders, and slow transit constipation. The Committee noted that slow transit constipation is the least prevalent subtype.
- 12.9. The Committee noted that there is no data available regarding the prevalence of slow-transit constipation in New Zealand. The Committee considered a meta-analysis which identified a pooled prevalence of chronic idiopathic constipation of 14% ([Suarez & Ford. Am J Gastroenterol. 2011;106:1582-91](#)), and a retrospective cohort study which identified a prevalence of slow-transit constipation of 4.3% among patients with chronic idiopathic constipation ([Nullens et al. Gut. 2012;61:1132-9](#)). The Committee considered that if these data are applicable to the New Zealand population, there may be as many as 30,000 individuals with chronic idiopathic constipation due to slow-transit constipation.
- 12.10. The Committee noted the gold-standard method for assessing colonic transit is the radio-opaque marker test. The Committee noted that there is variable access to colonic transit testing within New Zealand, and that slow-transit constipation is more often diagnosed using a combination of clinical observation, x-ray imaging, and familial history.
- 12.11. The Committee noted that the initial management strategy for symptomatic constipation is dietary modification, including fibre and fluid supplementation. The Committee noted that if this approach is inadequate, patients receive osmotic laxatives such as polyethylene glycol and lactulose, with stimulant laxatives such as bisacodyl used as a second-line treatment if osmotic laxatives do not adequately address the condition.
- 12.12. The Committee noted two meta-analyses which investigated the efficacy of pharmacologic treatment of chronic idiopathic constipation ([Ford et al. Gut. 2011;60:209-18](#); [Nelson et al. Gut. 2017;66:1611-22](#)). The Committee noted that Ford et al. (2011) concluded that prucalopride was superior to placebo for the treatment of chronic idiopathic constipation. The Committee noted that Nelson et al. (2017) reported no difference in primary endpoints for bisacodyl, sodium picosulphate, prucalopride, and velusetrag, but noted bisacodyl was superior in change from baseline in spontaneous bowel movements per week.
- 12.13. The Committee noted a systematic review which evaluated the cost effectiveness of treatment for chronic idiopathic constipation ([Han et al. Pharmacoeconomics. 2018;36:435-49](#)). The Committee noted that Han et al. (2018) reported that there is

limited evidence for the cost-effectiveness of treatments in patients who have not responded to laxatives.

12.14. The Committee noted evidence provided by the applicant from four randomised controlled trials:

- Multicentre, randomised, placebo-controlled, Phase 3 trial which investigated the efficacy and safety of prucalopride compared with placebo in 620 patients with severe chronic constipation (PRU-USA-11; [Camilleri et al. N Engl J Med. 2008;358:2344-54](#)).
- Multicentre, randomised, placebo-controlled, Phase 3 trial which investigated the efficacy and safety of prucalopride compared with placebo in 713 patients with severe chronic constipation (PRU-INT-6; [Tack et al. Gut. 2009;58:357-65](#)).
- Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial which evaluated the efficacy and safety of prucalopride compared with placebo in 641 patients with severe chronic constipation (PRU-USA-13; [Quigley et al. Aliment Pharmacol Ther. 2009;29:315-28](#)).
- Multicentre, randomised, double-blind, placebo-controlled Phase 3 trial which investigated the efficacy and safety of prucalopride compared with placebo in 303 elderly (≥ 65 years) with chronic constipation (PRU-INT-12; [Müller-Lissner et al. Neurogastroenterol. Motil. 2010;22:991-8](#)).

12.15. The Committee noted that the participants in these trials were generally older (median age 44 to 76 years) and predominantly female (70 to 91%).

12.16. The Committee considered that the results of these trials demonstrated a modest benefit with prucalopride compared with placebo in patients with chronic idiopathic constipation but noted that these results were not specific to individuals with chronic slow-transit constipation who had not responded to treatment with regular laxatives.

12.17. The Committee noted that these trials, and many others investigating the treatment of chronic idiopathic constipation, are placebo controlled. The Committee considered that this is not appropriate due to the availability of laxatives, and that new therapies for the treatment of chronic idiopathic constipation should be required to demonstrate equivalence or superiority to conventional laxatives.

12.18. The Committee noted that the adverse events reported to occur more frequently with prucalopride compared with placebo included headache, nausea, and diarrhoea. The Committee noted that while no significant increases in serious adverse events were reported in the clinical trials, there is limited long-term safety data available.

12.19. The Committee noted a randomised, double-blind, Phase 3 trial which investigated the efficacy and safety of macrogol/PEG 3350 plus electrolytes compared with prucalopride in 240 women with chronic constipation for whom laxatives have previously failed to provide adequate relief ([Cinca et al. Aliment Pharmacol Ther. 2013;37:876-86](#)). The Committee noted that the study concluded that macrogol/PEG 3350 plus electrolytes was at least as effective and generally better tolerated than prucalopride for the treatment of chronic constipation. The Committee considered that while this is an example of an active-controlled trial, that there were limitations that prevent its generalizability, including that it was a single-centre Eastern European study conducted in a controlled environment, with a large proportion of participants with an evacuation disorder at baseline, and a non-FDA endorsed primary endpoint.

- 12.20. The Committee considered that prucalopride would be used in conjunction with other agents such as conventional laxatives, and that funding prucalopride would be unlikely to reduce the use of other laxatives.
- 12.21. The Committee considered that the use of prucalopride has the potential to reduce longer-term complications of chronic constipation which can require surgical intervention, but that they did not review any evidence that supported this.
- 12.22. The Committee considered that there are a group of children and adolescents with dysmotility syndromes who could potentially benefit from treatment with prucalopride but noted that no evidence was considered for this population, and that this group is outside the Medsafe approved indication.
- 12.23. The Committee considered that individuals facing significant procedures such as intestinal transplant could still be considered via PHARMAC's Exceptional Circumstances Framework.
- 12.24. The Committee considered that the Gastroenterology services in New Zealand are overextended, and that it would be difficult to get an appointment with a gastroenterologist for chronic constipation.
- 12.25. The Committee considered that the Rome IV criteria for functional chronic constipation is adequate for defining the population with chronic idiopathic constipation but is not sufficient to identify patients with slow-transit constipation. The Committee considered that any restrictions on access to prucalopride would need to be specific to patients with slow-transit constipation who are refractory to regular laxatives.
- 12.26. The Committee considered that there is a high health need for patients with chronic slow-transit constipation for whom conventional laxatives have been inadequate but considered that the evidence provided by the applicant did not reflect this population. The Committee considered that the application should be referred back to the Gastroenterology Subcommittee regarding how to define the population with the highest health need and those most likely to benefit, and the evidence for the use of prucalopride in this population.

13. Methylnaltrexone subcutaneous injection for the treatment of intractable opioid-induced constipation in patients outside of palliative care

Application

- 13.1. The Committee reviewed a clinician application for the widening of access to methylnaltrexone bromide subcutaneous injection (Relistor) for the treatment of intractable opioid-induced constipation in patients outside of palliative care.
- 13.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 13.3. The Committee **recommended** that the funding of methylnaltrexone subcutaneous injection be widened to include patients with opioid-induced constipation outside of palliative care with a **low priority**.
- 13.4. The Committee **recommended** that the application be referred to the Gastrointestinal Subcommittee or the Analgesic Subcommittee for advice regarding the identification of the population with the highest health need and for advice regarding appropriate Special Authority criteria.

Discussion

- 13.5. The Committee noted that PTAC considered a funding application for methylnaltrexone subcutaneous injection for the treatment of opioid-induced constipation in patients receiving palliative care in [August 2016](#). The Committee noted that at this time, PTAC recommended that methylnaltrexone be funded with a high priority subject to restrictions limiting its use to the treatment of opioid-induced constipation in patients receiving palliative care where oral and rectal treatment are ineffective or unable to be tolerated. The Committee noted that PHARMAC funded methylnaltrexone subcutaneous injection for the treatment of opioid-induced constipation in patients receiving palliative care in January 2018.
- 13.6. The Committee noted that PHARMAC received a clinician application in September 2018 requesting that access to methylnaltrexone subcutaneous injection be widened to include patients with intractable opioid-induced constipation in non-palliative circumstances such as post-trauma or post-surgery.
- 13.7. The Committee noted that opioid-induced constipation is a common adverse effect associated with opioid use, and that chronic constipation can cause significant pain, has a negative impact on quality of life, and can lead to life-threatening complications such as faecal impaction and bowel perforation. Members noted that opioid-induced constipation can be so significant that opioid dose is reduced to alleviate the issue, which can compromise pain management.
- 13.8. The Committee noted that opioid-induced constipation is a significant problem in patients receiving palliative care, with a prevalence of approximately 47% of patients with cancer and 32% of patients who do not have cancer ([National health Needs Assessment for Palliative Care. Phase 1 Report: Assessment of Palliative Care Need. June 2011](#)). The Committee considered that there are factors other than opioid use that contribute to constipation in patients receiving palliative care (eg, dehydration, immobility, diet, polypharmacy). The Committee also considered that patients in palliative care are receiving higher doses of opioids than patients with non-palliative pain.
- 13.9. The Committee noted that the application requested funding for methylnaltrexone for use in hospital as a rescue therapy for intractable opioid-induced constipation following trauma or surgery; however, the Committee considered that methylnaltrexone has the potential to provide a benefit to a wider group of non-palliative patients, including patients receiving opioids for chronic non-cancer pain. The Committee considered that the evidence for use in this population should also be reviewed.
- 13.10. The Committee noted that opioid-induced constipation has a substantial impact on quality of life in patients with chronic non-cancer pain, and is associated with increased healthcare resource utilization and hospital costs following orthopaedic surgery ([Veiga et al. Pain Res Treat. 2018;5704627](#). [Alemayehu Value Health. 2014;17:A541](#). [Wittbrodt et al. J Pain Res. 2018;11:1017-25](#). [Christensen et al. Scand J Pain. 2016;11:104-110](#)).
- 13.11. The Committee noted that patients prescribed an opioid are often pre-emptively treated with stimulant laxatives and stool softeners. The Committee noted that if this is insufficient, opioid-induced constipation is treated with an escalating regime of osmotic laxatives and enemas. The Committee considered that the use of pre-emptive treatment means that intractable opioid-induced constipation requiring manual disimpaction occurs rarely.
- 13.12. The Committee noted that methylnaltrexone is a competitive antagonist of opioid receptor binding, with selectivity for the mu-opioid receptor. The Committee noted that as a quaternary amine, methylnaltrexone does not cross the blood-brain barrier and therefore does not impact opioid-mediated analgesic effects on the central nervous system.
- 13.13. The Committee noted that methylnaltrexone is Medsafe approved for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative

care when response to laxative therapy has not been sufficient. The Committee noted that the application being considered is for use outside of this indication (non-palliative care).

- 13.14. The Committee noted that methylnaltrexone is administered as a single subcutaneous injection on alternate days at a dose of 8 to 12 mg depending on patient weight. The Committee considered that a subcutaneous agent may be of benefit in patients who are unable to receive oral medications and can be administered by the patient or their caregivers with appropriate training.
- 13.15. The Committee noted that methylnaltrexone is the only peripherally acting mu-opioid antagonist available for use in New Zealand.
- 13.16. The Committee noted that PTAC previously considered evidence for the use of methylnaltrexone for the treatment of opioid-induced constipation in palliative care patients provided by two phase 3 trials: MNTX 301 ([Slatkin et al. J Support Oncol. 2009;7:39-46](#)) and MNTX 302 ([Thomas et al. N Engl J Med. 2008;358:2332-43](#)). The Committee noted that these trials did not include non-palliative patients but considered that the results demonstrate that subcutaneous methylnaltrexone does induced laxation in some patients. The Committee considered that there is no mechanistic reason methylnaltrexone would not be effective in non-palliative patients with opioid-induced constipation.
- 13.17. The Committee noted a double-blind, randomised, placebo-group Phase 2 trial which investigated the safety and efficacy of subcutaneous methylnaltrexone in 33 patients with acute opioid-induced constipation after orthopaedic procedures ([Anissian et al. J Hosp Med. 2012;7:67-72](#)). The Committee noted that more patients treated with methylnaltrexone achieved laxation compared with placebo (2 hours: 33.3% vs 0%, $P=0.0021$; 4 hours 38.9% vs 6.7%, $P=0.046$), and that time to laxation was shorter in patients treated with methylnaltrexone (15.8 hours vs 50.9 hours; $P=0.0197$). The Committee noted that more patients treated with methylnaltrexone expressed overall treatment satisfaction compared with patients treated with placebo (study endpoint: 83.3% vs 53.3%), and fewer patients treated with methylnaltrexone expressed dissatisfaction (0% vs 26.7%).
- 13.18. The Committee noted a double-blind, randomised, placebo-controlled study which investigated the effect of subcutaneous methylnaltrexone on opioid-induced constipation in 460 patients receiving opioids for chronic non-malignant pain ([Michna et al. J Pain. 2011;12:554-62](#)). The Committee noted that 34.2% of patients receiving methylnaltrexone had rescue-free bowel movements within 4 hours of dosing compared with 9.9% of patients receiving placebo ($P<0.001$), and patients receiving methylnaltrexone had significantly shorter time to first rescue-free bowel movement ($P<0.001$). The Committee noted that patients receiving methylnaltrexone reported greater improvement in patient-reported, constipation-specific quality of life at four weeks.
- 13.19. The Committee noted an open-label Phase 3 trial which investigated the long-term safety and efficacy of methylnaltrexone in 1034 patients with chronic non-cancer pain ([Webster et al. Pain Med. 2017;18:1496-1504](#)). The Committee noted that methylnaltrexone elicited a bowel movement within four hours in 34.1% of injections throughout the 48-week treatment period. The Committee noted that there was an improvement in mean weekly bowel movement rate, Bowel Movement Straining Scale score, Bristol Stool Scale score, and percentage of patients with complete evacuation.
- 13.20. The Committee noted a review and meta-analysis that included seven randomised controlled trials which investigated the efficacy and safety of methylnaltrexone for the treatment of opioid-induced constipation ([Seimens & Becker. Ther Clin Risk Manag. 2016;12:410-12](#)). The Committee noted that the study reported that patients treated with methylnaltrexone had more rescue-free bowel movements within 4 hours of the first

dose, had a higher stool frequency, and less time to laxation compared with placebo. The Committee noted that the study reported that patients receiving methylnaltrexone had a higher stool frequency and needed less time to laxation compared with placebo.

- 13.21. The Committee noted a systematic review and meta-analysis that included 27 placebo-controlled trials which investigated the efficacy of approved treatments for opioid-induced constipation, of which seven specifically looked at methylnaltrexone ([Nee et al. Clin Gastroenterol Hepatol. 2018;16:1569-84](#)). The Committee noted that the study reported that methylnaltrexone was significantly more efficacious than placebo for the treatment of opioid-induced constipation (RR 0.62; 95% CI 0.49 to 0.78; $P < 0.001$). The Committee noted that the study reported that patients with cancer-related pain had significantly better results favouring methylnaltrexone than patients with non-cancer-related pain. The Committee noted that only three of the trials investigating methylnaltrexone were conducted in patients who were refractory to conventional laxative treatment.
- 13.22. The Committee noted that the most common adverse effects associated with methylnaltrexone treatment are abdominal pain, nausea, and diarrhoea.
- 13.23. The Committee noted that the Health Quality & Safety Commission New Zealand (HQSC) has published a guidance document regarding reducing opioid-related harm, including an emerging care bundle on opioid-induced constipation (HQSC. [How-to guide: Reducing opioid-related harm through the use of care bundles](#)). The Committee considered that this demonstrates that the appropriate treatment of opioid-induced constipation is recognised by the HQSC as a priority in the reduction of opioid-related harm.
- 13.24. The Committee noted that the funding of methylnaltrexone has the potential to reduce emergency department and hospital admissions and may reduce the requirement for invasive procedures such as manual disimpaction; however, the Committee considered that there is limited evidence to support this for patients receiving chronic opioid treatment.
- 13.25. The Committee noted the applicant's suggestion that approximately 50 patients would be eligible for methylnaltrexone as rescue therapy for intractable opioid-induced constipation following trauma or surgery but considered that there is evidence that methylnaltrexone may provide a benefit in a wider group of non-palliative patients with intractable opioid-induced constipation.
- 13.26. The Committee considered that there is good quality evidence demonstrating that methylnaltrexone is more effective than placebo for the treatment of opioid-induced constipation for both palliative and non-palliative patients; however, the Committee considered that there would be significant fiscal risk associated with widening access to methylnaltrexone without restriction due to the large population that may be prescribed methylnaltrexone. The Committee therefore considered that the application should be referred to the Gastrointestinal Subcommittee or the Analgesic Subcommittee for advice regarding the population of patients with the highest health need and appropriate Special Authority criteria.

14. Glycomacropeptide-containing supplements and low protein foods for the dietary management of phenylketonuria

Application

- 14.1. The Committee reviewed a funding application from Cortex Health for glycomacropeptide-containing supplements and low protein foods for the dietary management of phenylketonuria.
- 14.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 14.3. The Committee **recommended** that glycomacropeptide-containing supplements for the dietary management of phenylketonuria be funded if **cost neutral** to the supplements for phenylketonuria already listed in Section D of the Pharmaceutical Schedule.
- 14.4. The Committee **recommended** that the low-protein foods supplied by Cortex Health be funded for the dietary management of phenylketonuria with a **medium priority**.

Discussion

- 14.5. The Committee considered advice regarding the application provided by Metabolic Specialists at the National Metabolic Service. This advice was sought by PHARMAC staff to assist in the Committee's review of the application due to the specialised requirements of patients with phenylketonuria (PKU).
- 14.6. The Committee noted that PTAC considered a funding application for sapropterin for the treatment of patients with PKU at risk of cognitive impairment in [August 2018](#). The Committee noted that at this time, PTAC recommended that PHARMAC consider broadening the range of dietary options and PKU supplements available on the Pharmaceutical Schedule.
- 14.7. The Committee noted that PKU is an autosomal inborn error of metabolism in which a deficiency or mutation in phenylalanine hydroxylase results in the inability to metabolize phenylalanine. The Committee noted that the degree of phenylalanine hydroxylase deficiency can vary among individuals with PKU and that the amount of residual phenylalanine hydroxylase activity dictates the severity of the resulting disorder.
- 14.8. The Committee noted that there are approximately 160 patients known to have PKU in New Zealand, and that dispensing data suggests that 105 patients are receiving supplements for PKU (79 of these on a regular basis).
- 14.9. The Committee noted that a restrictive diet low in phenylalanine is the cornerstone of management for PKU. The Committee noted that this requires patients to severely restrict the intake of all foods containing protein and to use supplements to ensure there is adequate intake of the other essential amino acids, vitamins, and minerals.
- 14.10. The Committee considered that dietary management of PKU is complex and difficult to maintain. The Committee considered that this can also be burdensome on the family and caregivers of children and adolescents with PKU ([MacDonald et al. Mol Genet Metab Rep. 2016;9:1-5](#)).
- 14.11. The Committee noted that inadequate management of PKU can result in the development of neurological disorders and intellectual disability.
- 14.12. The Committee noted a randomised, double-blind, placebo-controlled trial which reported that phenylalanine supplementation among adult patients with PKU had a negative effect on sustained attention and mood ([ten Hoedt et al. J Inherit Metab Dis. 2011;34:165-71](#)).

GMP-containing supplements

- 14.13. The Committee noted there are 19 formulations of amino-acid supplements currently funded for the dietary management of PKU (tablet, powder, infant formula, liquid, and oral semi-solid formulations).
- 14.14. The Committee noted that the supplements supplied by Cortex Health contain a protein formula made from glycomacropeptide (GMP) and five critical amino acids (tryptophan, arginine, leucine, histidine, and tyrosine). The Committee noted that GMP is a whole protein derived from whey that does not contain phenylalanine.

- 14.15. The Committee noted that the process of extracting and refining GMP results in the inclusion of trace quantities of phenylalanine in the supplements; however, the Committee considered that these amounts would have minimal impact for the majority of patients with PKU.
- 14.16. The Committee noted evidence for GMP-containing supplements provided by the following studies:
- 14.16.1. A two-stage, randomised crossover trial which investigated the efficacy and safety of a low-phenylalanine diet combined with GMP-medical foods or amino acid-medical foods in 30 subjects with early-treated PKU (Ney et al. *Am J Clin Nutr.* 2016;104:334-45).
 - 14.16.2. A retrospective longitudinal study which reported on the nutritional status of eleven patients with PKU receiving GMP-based protein substitutes and amino acid supplements (Pinto et al. *Eur J Clin Nutr.* 2017;71:1230-4).
 - 14.16.3. A prospective 6-month pilot study which investigated the effect of GMP compared with phenylalanine-free protein substitutes on blood phenylalanine control in 22 children with PKU (Daly et al. *J Hum Nutr Diet.* 2017;30:515-23).
 - 14.16.4. An inpatient metabolic study which assessed the ability of a GMP breakfast to promote satiety and affect plasma concentrations of AAs, insulin, and ghrelin in eleven subjects with PKU (MacLeod et al. *Mol Genet Metab.* 2010;100:303-8).
 - 14.16.5. A longitudinal, parallel, controlled study which evaluated the effect of a GMP formulation compared with a phenylalanine-free amino acid supplement on blood phenylalanine and tyrosine, and the biochemical nutritional status and growth of 48 children with PKU (Daly et al. *Orphanet J Rare Dis.* 2019;14:44).
 - 14.16.6. A 6-week randomised controlled cross-over study which investigated the impact of GMP compared with amino acids on blood phenylalanine variability in 18 children with PKU (Daly et al. *Nutrients.* 2019;11:pii E520).
 - 14.16.7. A systematic review and meta-analysis which evaluated intervention studies on the use of GMP supplementation in subjects with PKU (Pena et al. *Nutrients.* 2018;11:1794).
- 14.17. The Committee considered that these studies generally demonstrated that GMP-containing supplements are an acceptable protein substitute for patients with PKU and may have some advantages over amino acid supplements such as slower absorption, fewer side effects, and improved satiety.
- 14.18. The Committee noted that several of these studies reported that the GMP-containing supplements increase blood phenylalanine concentrations, and that dietary phenylalanine intake may need to be reduced to compensate for this. The Committee considered that this may be of importance for individuals with severe PKU.
- 14.19. The Committee noted the results of an unpublished taste and acceptability questionnaire conducted in New Zealand regarding two of the GMP-containing supplement products included in this application. The Committee noted that between 38% and 54% of patients preferred the GMP-containing products to their current supplement products.

Low-protein foods

- 14.20. The Committee noted there are 8 low-protein food products currently funded for the dietary management of PKU (baking mix and seven pasta varieties).

- 14.21. The Committee noted a study which reported that returning to a low-protein diet improved quality of life among patients with PKU ([Bik-Multanowski et al. J Inherit Metab Dis. 2008;31:S415-8](#)).
- 14.22. The Committee noted that the low-protein foods provided by Cortex Health include pasta, baking mix, substitute egg products, burger and chicken patty mix, cookies, and instant soups. The Committee considered that while there is no evidence that these specific food products provide a health benefit, it is reasonable to consider that more choice and convenience in food options has the potential to improve adherence with a low-protein diet.

General discussion

- 14.23. The Committee considered that poor palatability and the limited range of supplements and foods available may be adversely impacting adherence to a low-protein diet.
- 14.24. The Committee considered that access to GMP-containing supplements and additional low-protein food options would provide the most benefit for patients who are off diet or those having difficulty maintaining a low-protein diet due to taste fatigue or dislike of amino acid supplements.
- 14.25. The Committee noted that the advice from the Metabolic Specialists stated that funding GMP-containing supplements and additional low-protein foods may result in five to ten additional patients returning to diet and being dispensed supplements and low-protein foods.
- 14.26. The Committee noted that the distribution of bulky products with a short shelf-life and variable usage is challenging for community pharmacies. The Committee considered that a centralised distribution system for the supplements and low-protein foods may be preferable.
- 14.27. The Committee considered that there is adequate evidence that GMP-containing supplements are not inferior to amino acid formulations for supplying protein to individuals with PKU. The Committee also considered that broadening the range of low-protein foods available would provide a significant benefit for individuals with PKU.

15. Fluticasone furoate/umeclidinium/vilanterol for the treatment of chronic pulmonary disorder

Application

- 15.1. The Committee reviewed the application from GSK NZ Ltd for the funding of a combined inhaler containing fluticasone furoate / umeclidinium bromide / vilanterol trifenate (Trelegy Ellipta) for the management and treatment of Chronic Obstructive Pulmonary Disease (COPD).
- 15.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 15.3. The Committee **recommended** that fluticasone furoate (FF) / umeclidinium bromide (UMEC) / vilanterol trifenate (VI) (Trelegy Ellipta) be listed as **cost neutral** to future prices of triple therapy agents that include an inhaled corticosteroid (ICS), long-acting beta-adrenoceptor agonist (LABA) and long-acting muscarinic antagonist (LAMA) that are listed on the Pharmaceutical Schedule as either individual components or as combination inhalers.

Discussion

- 15.4. The Committee noted that COPD attributes the third and fourth highest loss of health in New Zealand in males and females, respectively (NZ Ministry of Health 2016) and is the second leading cause of amenable mortality in New Zealand (NZ Ministry of Health 2018).
- 15.5. The Committee noted that the Impact of Respiratory Disease in New Zealand: 2016 update report estimated that in 2015 there were nearly 37,000 New Zealanders living with severe and ever-hospitalised COPD. The Committee noted that approximately 96% of COPD cases are in those over the age of 45, making the population prevalence of severe and ever-hospitalised COPD 1.9% in people aged 45 and over.
- 15.6. The Committee noted that Māori and Pacific populations have higher rates of COPD at 3.7 times and 2.8 times the non-Māori, non-Pacific and non-Asian rate (non-MPA), respectively. Members noted that Māori and Pacific populations also have higher rates of morbidity and mortality, and develop COPD significantly earlier: the average age of Māori with COPD was 63.4 years, compared with 66.2 for Pacific peoples, 69.7 for Asian peoples, and 73.3 for individuals with other ethnicities (Barnard and Zhang, The Impact of Respiratory Disease in New Zealand: 2016 update).
- 15.7. The Committee noted that a high degree of inequity across both the socio-economic spectrum and different ethnic groups has been observed for COPD. The Committee noted that COPD rates are 5.7 times higher in the most deprived NZDep quintile than in the least deprived, with the gradient persisting across Māori, Pacific, Asian and non-MPA ethnic groups.
- 15.8. The Committee noted that Trelegy Ellipta contains an inhaled corticosteroid (ICS), long-acting beta-adrenoceptor agonist (LABA) and long-acting muscarinic antagonist (LAMA) in one inhaler. Members noted that Trelegy Ellipta contains 100mcg fluticasone furoate, 62.5mcg umeclidinium bromide and 25mcg vilanterol trifenate, powder for inhalation.
- 15.9. The Committee noted that prior to 2016, LABA and ICS (as single inhalers or in combination) were easier to access/prescribe than LAMA (which required severe COPD confirmed by spirometry), which may have meant that ICS has been prescribed inappropriately for patients with mild-moderate COPD.
- 15.10. The Committee reviewed the NICE 2018 guidelines (NICE 2018. Chronic obstructive pulmonary disease in over 16s: diagnosis and management: www.nice.org.uk/NG115) for non-pharmacological management and use of inhaled therapies for COPD and noted that the treatment paradigm steps up from 1. short-acting beta-adrenoceptor agonists(SABA)/short-acting muscarinic antagonists (SAMA), then 2. LAMA, LABA, both LAMA and LABA used in combination, and only then 3. an ICS is introduced. The Committee noted that the use of ICS in COPD management is less clear than LABA and LAMA therapy, and noted that most guidelines advise triple therapy for severe COPD (GOLD D: ≥ 2 courses of oral steroids per year or ≥ 1 hospital admission per year and more symptoms [mMRC ≥ 2 or CAT ≥ 10]). Members noted that the use of ICS in COPD is associated with higher rates of pneumonia.
- 15.11. The Committee noted the supplier has advised that the pivotal evidence for the use of Trelegy Ellipta is provided by the IMPACT trial (Lipson et al. N Engl J Med. 2018;378:1671-80). Members noted that the IMPACT trial was a large Phase 3 randomised control trial of high quality. The Committee noted that the trial compared triple therapy with FF/UMEC /VI (ICS + LAMA + LABA) vs dual therapy with VI/FF (LABA + ICS) or with UMEC/VI (LAMA + LABA) and each intervention was administered in a single Ellipta inhaler. The Committee considered that dual therapy was the wrong comparator for the study and the appropriate comparator would have been triple therapy administered as separate components. Members noted that the rate of moderate or severe exacerbation per year was 0.91 with triple therapy vs 1.07 (FF + VI, $p < 0.001$) vs

1.21 (UMEC + VI, $p < 0.001$), and the mean change from baseline trough forced expiratory volume (FEV1) between ICS/LABA/LAMA and ICS/LABA was 97ml and LAMA/LABA was 54ml (noting that the minimal clinically important difference [MCID] was 100 mLs).

- 15.12. The Committee reviewed the health-related quality of life (HRQoL) data from the Lipson et al publication and noted that the mean change from baseline was -5.5 for triple therapy vs -3.7 for both dual therapy combinations, noting that the Minimally Clinically Important Difference (MCID) was 5 on 0-100 score. Members noted that the rate of pneumonia was more than 50% higher with ICS-containing inhalers than with the LAMA/LABA combination (9.6 vs. 6.1 per 100 patient-years). Members noted that a greater reduction in exacerbation rate with triple therapy was observed for patients with eosinophils >150 cells/ μ L.
- 15.13. The Committee noted that 38% of patients enrolled in the trial were already receiving treatment with triple therapy and approximately 70% were receiving an inhaled glucocorticoid prior to enrolment. Members noted that patients with a history of asthma were included, and considered that of the LAMA/LABA group, many would have abruptly stopped their ICS at randomization. Members considered this could explain the early upsurge in exacerbations in that group and may explain the finding that ICS/LABA group had fewer exacerbations than the LAMA/LABA group, which is a different finding than was reported in the FLAME trial (Wedzicha et al. *N Eng J Med.* 2016;374:2222-34).
- 15.14. The Committee also reviewed the results of the FULFIL trial (Lipson et al. *Am J Respir Crit Care Med.* 2017;196:438-46) that compared once daily triple therapy as Trelegy vs twice daily FF/budesonide (ICS + LABA). Members noted that mean changes from baseline in FEV1 were 142 ml for patients administered Trelegy vs -29 ml for patients administered the dual therapy, and mean changes from baseline in St George's Respiratory Questionnaire (SGRQ) scores were -6.6 and -4.3, respectively.
- 15.15. The Committee considered that there are numerous ICS, LABA, LAMA, LABA/LAMA and ICS/LAMA inhalers listed on the Pharmaceutical Schedule that would have the same effect as Trelegy when used in appropriate combinations, and therefore funding Trelegy would not address an unmet health need.
- 15.16. The Committee considered that the patient number estimates provided by the supplier were underestimated and considered that over 50% of patients with COPD currently on triple therapy would be likely to change to a single inhaler.
- 15.17. Members noted that there is some evidence from an open-label, sponsor-designed, cross-over study that reported patient preference, reduced instruction time and less critical errors (errors likely to result in no or significantly reduced medication being inhaled) with the Ellipta inhaler device (van der Palen et al. *Int J of COPD.* 2018;13:2515-23).
- 15.18. The Committee reviewed a non-inferiority study of once daily FF/VI /UMEC (using a single inhaler) vs FF/VI and UMEC (using two inhalers) and noted that the single inhaler was found to be non-inferior to treatment with two inhalers in change from baseline of trough FEV1 after 24 weeks, and secondary endpoints, including exacerbation rates and HR-QoL (Bremner et al. *Respir Res.* 2018;19:19).
- 15.19. Members noted that patients with severe (GOLD D) COPD that are mixing up their inhalers may benefit from a single inhaler therapy.
- 15.20. The Committee considered that there are risks of side-effects, including pneumonia, with high dose ICS and noted that the fluticasone foroate 100 mcg provided per inhalation in the Trelegy inhaler is equal to 500 mcg fluticasone propionate and would therefore be considered a very high dose of ICS.

- 15.21. The Committee considered that there was some clinical concern regarding triple therapy, and noted that an editorial by Suissa and Drazen, (N Eng J Med. 2018;378:1723-24) cautions that “although single-inhaler triple therapy offers simplicity in treating COPD, any potential benefit could be lost and potential undue harm induced if triple therapy is expanded to patients with GOLD groups A, B, and C COPD”.
- 15.22. The Committee considered a double-blind, parallel group study (the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management [WISDOM] trial) (Magnussen et al. N Eng J Med. 2014;271:1285-94) investigating whether patients with COPD receiving both LAMA and LABA therapy with inhaled glucocorticoids would have similar outcomes regardless of whether the glucocorticoids were withdrawn or continued. Members noted that there was no difference in the primary end point of exacerbations but a significant 43 mL (MCID 100ml) mean fall in FEV1 after ICS withdrawal and no difference in pneumonia incidence. The Committee noted that post hoc analysis revealed a 43% increase in exacerbations after ICS withdrawal in those patients who had blood eosinophils of at least 300 cells/ μ L in conjunction with two or more exacerbations in the past year, whereas there was no difference in patients with eosinophils less than 300 cells/ μ L.
- 15.23. The Committee considered that there was high quality (GRADE 1) evidence that Trelegy is superior to dual therapy with ICS/LABA and LAMA/LAMA for rate of exacerbations, minor improvements in HRQoL and trough FEV1 favouring Trelegy. However, Members considered that the pivotal trial does not answer the question of how Trelegy compares to triple therapy with multiple inhalers for severe COPD, as is standard of care in NZ at present.
- 15.24. The Committee acknowledged that severe COPD impacts on the quality of life for family/whanau but considered that there was no evidence that single inhaler therapy produces health benefit for family/whanau/society over multiple inhalers.
- 15.25. The Committee considered that there is a risk is that prescribers/patients will switch to the single inhaler product, resulting in reduced opportunities for savings on other inhaled medicines for COPD that could be used to invest in other medicines. Members considered that the all in one triple therapy inhaler would not provide an added health benefit that is not addressed through currently funded products, and no premium should be paid for the combined product.
- 15.26. The Committee considered that Trelegy Ellipta would be used in combination with short-acting beta-adrenoceptor agonist inhalers, intermittent oral corticosteroids and with or without antibiotics. Members noted that Trelegy Ellipta would replace dual inhalers for patients already on triple therapy (ICS/LABA + LAMA combination or ICS + LAMA/LABA combination) and raised concern that it would replace LAMA/LABA as step up therapy.
- 15.27. The Committee considered that Trelegy Ellipta would not be appropriate as an initial therapy for COPD and considered that if it were to be open listed, patients with mild to moderate COPD would be starting on treatment with an ICS. The Committee requested that PHARMAC seek advice from the Respiratory Subcommittee to whether Special Authority criteria should be put in place to restrict use to COPD patients with severe disease to prevent inappropriate prescribing.
- 15.28. The Committee considered that there was no evidence base to support device delivery systems as a way to improve equity in COPD. Members considered that there are a number of other issues that are more important to address, such as accessibility of pulmonary rehabilitation programs, influenza vaccination, education, access to services and smoking cessation. Members were not convinced that adherence arguments could be used as a substitute for real life outcomes and considered that if adherence made a huge difference to COPD outcomes, that this would be reflected in the trials.

16. Capsaicin Cream 0.075% cream for the treatment of cannabinoid hyperemesis syndrome

Application

- 16.1. The Committee reviewed an application from a clinician for capsaicin cream 0.075% for the treatment of cannabinoid hyperemesis syndrome.
- 16.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 16.3. The Committee **recommended** that capsaicin cream 0.075% for the treatment of cannabinoid hyperemesis syndrome be **declined** based on limited evidence of benefit, an unclear mechanism of action of the treatment in the proposed indication and funded alternatives.

Discussion

- 16.4. The Committee considered [data released by the Ministry of Health](#) which reported that 11% of adults aged 15 years and older reported using cannabis in the last 12 months. Of these, 34% reported using cannabis at least weekly. Māori men and women were significantly more likely to report cannabis use compared to non-Māori men and women, as were adults living in the most deprived areas compared to adults living in the least deprived areas.
- 16.5. The Committee considered a single-centre study by [Habboushe J et al. \(Basic Clin Pharmacol Toxicol 2018;122:660-2\)](#). The Committee noted that this study investigated the prevalence of cannabinoid hyperemesis syndrome, among 155 people reporting marijuana usage 20 or more days per month, and that 51 (32.9%) were categorised as having experienced mild-severe cannabinoid hyperemesis syndrome symptoms in the past 6 months. The Committee considered that the authors of this study reported a number of limitations, including the potential for under-reporting of marijuana use which may have introduced bias to the sample.
- 16.6. The Committee considered that the epidemiology of cannabinoid hyperemesis syndrome is not well characterised, but that based on the available published literature and the estimated number of weekly cannabis users in NZ, up to ~32,000 New Zealanders could have experienced cannabinoid hyperemesis syndrome at some level of severity in the last 6 months. The Committee considered that the true prevalence of cannabinoid hyperemesis syndrome has potential to increase over time with increasing recreational and/or medicinal use of cannabinoids. Furthermore, the Committee considered that increased recognition of the syndrome may lead to increased diagnosed prevalence in future.
- 16.7. The Committee considered that based on anecdotal reports from different DHB hospital emergency departments there could be roughly 2000 – 4000 presentations to emergency departments or after hours clinics for cannabinoid hyperemesis syndrome in New Zealand each year.
- 16.8. The Committee considered a case series of 98 patients with cannabinoid hyperemesis syndrome ([Simonetto et al. Mayo Clin Proc. 2012;87:114-9](#)) and noted that cannabinoid hyperemesis syndrome is characterised by paradoxical, intractable vomiting on a background of chronic marijuana use. A pathognomonic feature is temporary relief of symptoms with compulsive use of hot-water bathing.
- 16.9. The Committee considered a systematic review describing the pharmacologic treatment of cannabinoid hyperemesis syndrome ([Richards JR et al. Pharmacotherapy 2017;37:725-34.](#)). The Committee noted that cannabinoid hyperemesis syndrome is associated with frequent emergency department presentations and diagnostic delay.

The Committee noted that patients with cannabinoid hyperemesis syndrome typically receive multiple diagnostic tests and procedures, with symptoms generally refractory to standard treatments. The Committee noted that cannabinoid hyperemesis syndrome has also been associated with further sequelae, including acute renal failure. The Committee considered that anecdotal reports from NZ clinicians suggest that patients presenting with cannabinoid hyperemesis syndrome are often extremely distressed, are slow to discharge from the emergency department or require hospital admission.

- 16.10. The Committee noted that a number of authors have concluded that the most effective treatment for cannabinoid hyperemesis syndrome appears to be cannabis cessation ([Sorensen CJ et al. J Med Toxicol 2017;13:71-87.](#), [Richards JR et al. Pharmacotherapy 2017;37:725-34.](#), [Lapoint J et al. West J Emerg Med 2018;19:380-6.](#)). The Committee considered that other treatments considered for use are supportive care with intravenous fluids, benzodiazepines and dopamine antagonists. The Committee considered that currently funded anti-emetics (including ondansetron, cyclizine and metoclopramide), have been reported to be often ineffective ([Richards JR et al. Pharmacotherapy 2017;37:725-34.](#)); and, that intravenous haloperidol has some limited evidence of efficacy ([Sorensen CJ et al. J Med Toxicol 2017;13:71-87.](#), [Richards JR et al. Pharmacotherapy 2017;37:725-34.](#)). The Committee considered that the evidence in support of the treatments for cannabinoid hyperemesis syndrome was of poor quality.
- 16.11. The Committee considered that current treatment approaches in New Zealand include cannabis cessation, intravenous fluids, high dose haloperidol and antiemetics in addition to hot showers. The Committee considered that anecdotal reports from NZ clinicians suggested that the current treatment options are considered to have limited efficacy and that the addition of capsaicin cream to the therapeutic armamentarium would lead to shorter length of stays, more self-management at home and lower risks of treatment toxicity. The Committee considered that some NZ clinicians are suggesting patients purchase capsaicin cream over the counter to manage the symptoms of cannabinoid hyperemesis syndrome.
- 16.12. The Committee considered that one 45g tube of capsaicin cream would allow for at least 1.5 applications of capsaicin cream to the entire body. The Committee considered that the application area for cannabinoid hyperemesis syndrome would be smaller than the entire body and therefore 1 tube would likely be sufficient for one patient per cannabinoid hyperemesis syndrome episode.
- 16.13. The Committee considered that there would be community use of capsaicin cream but that funding could be limited to the hospital setting to allow use in the emergency department setting, with additional tubes purchased from a pharmacy if required.
- 16.14. The Committee considered three published case reports/series that provide the primary evidence for the health benefits of capsaicin cream for the treatment of cannabinoid hyperemesis syndrome:
 - 16.14.1. A case series published by [Dezieck L et al. \(Clin Toxicol 2017;55:908-13\).](#) described 13 cases of suspected cannabinoid hyperemesis syndrome treated with capsaicin cream. All 13 patients experienced symptom relief after administration of capsaicin cream, with a median time to discharge of 216 minutes. Some patients (not quantified) found burning sensation intolerable resulting in refusal of further dosing.
 - 16.14.2. A case series published by [Graham J et al. \(Pediatrics 2017;140:e20163796\).](#) described 2 cases of diagnosed cannabinoid hyperemesis syndrome in adolescent patients treated with capsaicin cream. Both patients experienced abdominal pain and nausea symptom improvement after administration of capsaicin cream. Both patients reported a burning sensation.

- 16.14.3. A case study published by [Moon AM et al. \(ACG Case Rep J 2018;5:e3\)](#), described a patient with diagnosed cannabinoid hyperemesis syndrome whose symptoms improved with capsaicin cream. The patient reported burning of the skin.
- 16.15. The Committee considered that the evidence to support the use of capsaicin cream in the management of cannabinoid hyperemesis syndrome was limited to a small number of case studies, was of poor quality, and that a randomised controlled trial would be needed to demonstrate efficacy in comparison to alternative funded treatments.
- 16.16. The Committee noted that capsaicin cream has not been approved by Medsafe for the treatment of cannabinoid hyperemesis syndrome. The Committee considered that the mechanism of action of capsaicin cream in cannabinoid hyperemesis syndrome was unclear and would not support empirical use.
- 16.17. The Committee suggested that NZ clinicians involved in the management of cannabinoid hyperemesis syndrome could investigate the option of conducting a small study to demonstrate the efficacy of capsaicin cream in comparison to alternative treatments in the New Zealand clinical setting.
- 16.18. The Committee considered that randomised controlled trial evidence of treatment effect would be needed to justify a positive recommendation for the funding of capsaicin cream for cannabinoid hyperemesis syndrome.