

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 1 & 2 November 2018

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.

	<i>Present:</i>	3
1	Subcommittee Minutes	3
	<i>Mental Health Subcommittee</i>	3
	<i>Nephrology</i>	3
	<i>Neurological</i>	4
	<i>Immunisation</i>	4
2	Correspondence & Matters Arising	4
	<i>Multiple Sclerosis – Widening Access Application</i>	4
	<i>Correspondence from supplier on collagenase clostridium histolyticum</i>	6
3	Benzocaine 18%/tetracaine hydrochloride 2% (ZAP Topical Anaesthetic Gel) and lidocaine (25 mg/g)/prilocaine (25 mg/g) (Oraqix) as topical local anaesthetic gels for dental use	7
4	Calcipotriol with betamethasone foam spray for the treatment of psoriasis vulgaris	10
5	Abiraterone acetate for the treatment of high-risk metastatic hormone-naïve prostate cancer and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer	13
6	Olaparib for the maintenance treatment of platinum-sensitive BRCA-mutated relapsed ovarian cancer	18
7	Pembrolizumab for the treatment of metastatic non-small cell lung cancer in combination with chemotherapy	20
8	Nivolumab for the treatment of relapsed clear cell renal cell carcinoma	24
9	Denosumab for the treatment of hypercalcaemia of malignancy or malignant bone disease in patients with severe renal impairment	26
10	Evolocumab for the treatment of high-risk hypercholesterolaemia (homozygous and heterozygous familial hypercholesterolaemia)	30
11	Whole thyroid extract and normal and extended release T3 for the treatment of hypothyroidism	32

Present:

PTAC members:

Mark Weatherall (Chair)

Marius Rademaker (Deputy Chair)

Alan Fraser

Ian Hosford

Jane Thomas

Jennifer Martin

Matthew Strother (Friday 2 November 2018 only)

Melissa Copland

Sean Hanna

Simon Wynn Thomas (from 2pm, Thursday 1 November 2018 onward)

Stephen Munn

Stuart Dalziel

Tim Stokes

1 Subcommittee Minutes

Mental Health Subcommittee

- 1.1 The Committee reviewed and accepted the minutes of the Mental Health Subcommittee of PTAC meeting held on 12 June 2018. For completeness, where PTAC had additional comments, these are noted below.
- 1.2 The Committee noted that the key issues with methylphenidate prescribing had been identified by the Subcommittee. PTAC was in agreement with the issues minuted and considered the precautionary approach taken by the Subcommittee to be appropriate.
- 1.3 The Committee asked that any communications about the pending doxepin discontinuation be provided to all prescribers as this medicine is often used for non-psychiatric indications.
- 1.4 The Committee noted that Janssen had provided updated patent information about its paliperidone 1-monthly depot injection.

Nephrology

- 1.5 The Committee noted the record of the Nephrology Subcommittee meeting held 20 March 2018. The Committee noted and accepted the recommendation related to paragraph 7.4 regarding long-acting erythropoietin.
- 1.6 The Committee noted the Subcommittee's view regarding cinacalcet. The Committee agreed with the view of the Subcommittee, and has previously noted, that patients with renal failure on renal replacement therapy have unmet health needs, and in some patients, this is related to symptomatic hyperparathyroidism. However, with poor evidence of improvement with use of cinacalcet in health outcomes important to patients such as mortality, health-related quality of life, or health conditions such as bone pain or fractures; the Committee considered that it would be very difficult for PHARMAC to model health gains from cinacalcet in a way that would rank the proposal for cinacalcet favourably against unfunded agents for other conditions. The Committee considered that more robust evidence of effectiveness would be required to modify its recommendation.

- 1.7 The Committee noted that a funding application was being prepared by Subcommittee members for the use of cinacalcet in the post-renal transplant setting for patients with severe hypercalcaemia requiring treatment as a bridge to parathyroidectomy and look forward to considering this application at a future meeting.
- 1.8 The Committee noted the Subcommittee's recommendation in paragraph 6.3 that sevelamer carbonate be listed with a medium priority; however, the Committee considered it should review this funding application at a future PTAC meeting. The Committee considered it would be useful to include further information regarding cost effectiveness analysis and updated patent information in the briefing paper.
- 1.9 The Committee noted and accepted the remainder of the record of the meeting.

Neurological

- 1.10 The Committee reviewed the Neurology Subcommittee minutes from the 4 July 2018 meeting.
- 1.11 The Committee noted that it had requested the view of the Neurology Subcommittee and the Multiple Sclerosis Treatment Assessment Committee (MSTAC) on a funding application for ocrelizumab for relapsing remitting multiple sclerosis (RRMS) and an application to widen access to the currently funded multiple sclerosis treatments. The Committee noted that it would be considering the following recommendations from the Neurological Subcommittee: 6.2, 8.3, 8.4, 8.5, 8.6, 8.12, 8.13, and the advice provided by MSTAC in relation to these applications in the Matters Arising section of the meeting.
- 1.12 The Committee noted and accepted the remaining recommendations of the Neurological Subcommittee, 2.2, 6.14 and 7.4.

Immunisation

- 1.13 The Committee reviewed the Immunisation Subcommittee minutes from the 16 May 2018 meeting.
- 1.14 The Committee noted that the Immunisation Subcommittee reviewed a funding application for a meningococcal B vaccine, 4CMenB (Bexsero) and made recommendations 8.3 and 8.4. The Committee considered that there was a lack of clarity in the way the UK Joint Committee on Vaccination and Immunisation (JCVI) assessed the cost effectiveness of 4CMenB. The Committee considered that it should consider this funding application at its next meeting.
- 1.15 The Committee noted and accepted the remaining recommendations of the Immunisation Subcommittee, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8 and 7.3.

2 Correspondence & Matters Arising

Multiple Sclerosis – Widening Access Application

- 2.1 The Committee reviewed a paper from PHARMAC staff summarising the view of the Neurological Subcommittee and the Multiple Treatments Assessment Committee (MSTAC) on funding applications for ocrelizumab for relapsing remitting multiple sclerosis (RRMS), ocrelizumab for primary progressive multiple sclerosis (PPMS) and widening access to a currently funded Multiple Sclerosis (MS) treatments.

- 2.2 The Committee noted that three of the Neurological Subcommittee members had declared conflicts of interest relating to MS treatments. The Committee noted that the conflicts had been considered at the Subcommittee meeting and as a result, with regards to ocrelizumab, there was one member that had to abstain from the consensus recommendation but was able to participate in the discussion. The Committee noted that all three members were permitted to participate in the widening access to MS treatments discussion and consensus discussion.

Ocrelizumab for RRMS

- 2.3 The Committee noted that at its February 2018 meeting it had recommended listing ocrelizumab for RRMS if it was cost-neutral to other funded MS treatments. The Committee noted that it had requested that the Neurological Subcommittee and MSTAC be asked for their views on the risk of using ocrelizumab in JCV positive patients, the likely fiscal risks associated with adding an additional line of therapy, and treatment sequencing options for ocrelizumab.
- 2.4 The Committee noted that the Neurological Subcommittee recommended ocrelizumab be listed with a medium priority; and, that the Subcommittee considered that there was likely to be a benefit for patients who are JCV positive, but that it is difficult to define the magnitude of the benefit.
- 2.5 The Committee considered that no direct comparison studies were available comparing the effectiveness of ocrelizumab to the 'newer' MS treatments (natalizumab, fingolimod, dimethyl fumarate, teriflunomide), but based on indirect comparisons, the Committee considered that it was likely ocrelizumab has similar, but not superior, efficacy to the 'newer' MS treatments.
- 2.6 The Committee considered that in the absence of evidence to support a greater health benefit than the currently funded 'newer' MS treatments that it did not support a change to its previous recommendation. The Committee clarified its recommendation was that ocrelizumab for the treatment of RRMS be funded if it was cost-neutral to the other funded newer MS treatments (natalizumab, fingolimod, dimethyl fumarate, teriflunomide). The Committee noted that there are a number of funded MS treatments and that if further evidence was provided to support a health benefit of treatment with ocrelizumab compared to the currently funded MS treatments, for patients who are JCV positive, then it would be happy to reconsider its recommendation. The Committee thanked the Neurological Subcommittee and MSTAC for their views on this matter.

Ocrelizumab for PPMS

- 2.7 The Committee noted MSTAC's view that ocrelizumab should be funded for primary progressive multiple sclerosis (PPMS) in patients with active inflammatory disease. The Committee considered that there is a high unmet health need in patients with PPMS; however, it would need to see more robust evidence of improved health outcomes to change its recommendation that the application be declined.

Widened Access to currently funded MS Treatments

Definition of Significant relapse

- 2.8 The Committee noted that the Neurological Subcommittee had recommended that the application to amend the definition of Significant Relapse be declined and that MSTAC shared the same view. The Committee accepted this recommendation.

Alternative Measurement Scales

- 2.9 The Committee noted that the Neurological Subcommittee recommended that the application to use alternative measurement scales be declined and that MSTAC shared the same view. The Committee accepted this recommendation.

Clinically Isolated Syndrome (CIS)

- 2.10 The Committee noted that the Neurological Subcommittee recommended that consideration be given to targeting a subgroup of McDonald positive CIS patients with a worse prognosis, to have early treatment; and, that the Subcommittee proposed the following criteria: oligoclonal band (OCB) positive, OR more than 10 lesions at baseline OR a further new lesion within the first six months of diagnosis with McDonald positive MS. The Committee noted that MSTAC shared a similar view.
- 2.11 The Committee noted that the McDonald criteria, which are used to aid in the diagnosis of clinically definite MS (CDMS), had undergone a recent revision (2017) and that this revision allows that a positive oligoclonal band (OCB) test may substitute for MRI dissemination in time (DIT).
- 2.12 The Committee considered that the revised McDonald criteria allow for earlier diagnosis of CDMS but that it had not seen good quality evidence that earlier treatment, at the stage of CIS, improves long-term health outcomes. The Committee considered that at this time it did not support a positive recommendation to fund treatment for CIS. However, the Committee considered that it was important that should new evidence become available that this recommendation should be reviewed.

Stopping Criteria

- 2.13 The Committee considered that removing the EDSS gradient scale would reduce the administration burden for neurologists however it was uncertain as to the additional health benefit that would be gained as a result. The Committee considered that the reasons for the Stopping Criteria were both financial and clinical; due to the disability progression endpoints that were used in the pivotal trials for the new agents.
- 2.14 The Committee considered MSTAC's view that the stopping criteria be amended to reaching EDSS 4.5 for all patients, and the Neurological Subcommittee recommendation that the stopping criteria be amended to stopping on reaching EDSS 6.0 for all patients.
- 2.15 The Committee recommended that PHARMAC staff conduct analysis to determine what the financial impact would be of amending the stopping criteria to 4.5, 5.5 and 6.0 for all patients and bring this back to the Committee for its view. The Committee considered that the financial impact of widening access, and its view of this, could then be provided to both the Neurological Subcommittee and MSTAC for their views.

Correspondence from supplier on collagenase clostridium histolyticum

- 2.16 The Committee reviewed correspondence from supplier of collagenase clostridium histolyticum (CCH).
- 2.17 The Committee noted that at its previous meeting it had considered that, overall, that CCH is probably equivalent in efficacy to fasciotomy, in terms of initial response to treatment, and considered that CCH is probably not as good as fasciectomy. The Committee considered

the correspondence from the supplier but felt that this advice still reflected the evidence provided.

- 2.18 The Committee noted the applicant's request for the source of recurrence rates. The Committee noted this had been sourced from the NICE report TA459, section 3.19.
- 2.19 Members also discussed two other studies of CCH, including Eaton et al 2014 Plastic and Reconstructive Surgery 133:5;1241-51, and Leafblad et al 2018 American Society for Peripheral Nerve (poster only)

3 Benzocaine 18%/tetracaine hydrochloride 2% (ZAP Topical Anaesthetic Gel) and lidocaine (25 mg/g)/prilocaine (25 mg/g) (Oraqix) as topical local anaesthetic gels for dental use

Application

- 3.1 The Committee considered two funding applications for topical local anaesthetic gels for dental use:
- 3.2 An application from HealthCare Essentials Ltd for the listing of benzocaine 18%/tetracaine hydrochloride 2% (ZAP Topical Anaesthetic Gel) on the Hospital Medicines List.
- 3.3 A clinician application for the listing of benzocaine 18%/tetracaine hydrochloride 2% (ZAP Topical Anaesthetic Gel) and lidocaine (25 mg/g)/prilocaine (25 mg/g) (Oraqix) on the Hospital Medicines List.
- 3.4 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 3.5 The Committee **recommended** that the application for benzocaine 18%/tetracaine hydrochloride 2% (ZAP Topical Anaesthetic Gel) be declined based on insufficient evidence of efficacy and safety.
- 3.6 The Committee **recommended** that the application for lidocaine (25 mg/g)/prilocaine (25 mg/g) (Oraqix) be declined based on low health need, insufficient evidence of benefit, and relatively high cost, compared with lidocaine 2.5%/prilocaine 2.5% cream (EMLA), a funded comparator with the same composition of active substances.

Discussion

- 3.7 The Committee noted that the clinician applicant estimated that approximately 400,000 children, adolescents, and adults per year are treated with topical anaesthetics as part of their dental care through DHB oral health services in New Zealand. The Committee considered that PHARMAC should write to the Ministry of Health to verify these estimates and request data on the number of scaling and deep root-planing procedures conducted in children. In addition, the Committee suggested that PHARMAC make contact with the Dental Council and the University School of Dentistry to help with estimates of patient numbers for any future applications.
- 3.8 The Committee considered that topical anaesthetic agents are primarily used before injectable local anaesthetics are administered in order to make the injection more tolerable. The Committee considered that this technique is commonly used in children requiring

injectable anaesthesia and approximately 30% of adults requiring injectable anaesthesia in private practice, and in 90% of all patients receiving hospital dental care.

- 3.9 The Committee noted that currently funded topical anaesthetic preparations included on the Hospital Medicines List (HML) include benzocaine gel 20%, tetracaine gel 4%, lidocaine gel 2%; and lidocaine 2.5%/prilocaine 2.5% either as a cream or patch (EMLA). The Committee considered that lidocaine gel 2% is the agent most commonly used by hospital dentists.
- 3.10 The Committee noted the results of a prospective clinical trial which investigated the effectiveness of topical benzocaine 20% compared with placebo (normal saline) in relieving pain and stress in patients following deep cavity restoration and extraction of teeth under local anaesthesia ([Al-Samadani & Gazal. Saudi Med J. 2015;36:1342-7](#)). The Committee noted that the mean (SD) preoperative stress levels (measured on a visual analogue scale [VAS]) were 37.00 (20.63) in the benzocaine group compared with 37.17(17.47) in the normal saline group (P=0.97), and that the mean (SD) postoperative stress levels were 8.67 (11.00) in the benzocaine group compared with 27.61(22.82) in the normal saline group (P=0.002). The Committee also noted that there was a significant difference in mean pain scores between treatment groups post buccal injection (normal saline 44.57 [18.2] vs benzocaine 14.67 [16.18]; P=0.001), post palatal injection (normal saline 47.89 [23.47] vs benzocaine 19.17 [16.61]; P=0.01), and post inferior alveolar nerve block (normal saline 47.50 [19.49] vs benzocaine 11.11 [7.82]; P=0.02). The Committee considered that the results of this study demonstrated that the use of a topical local anaesthetic gel reduces post-operative stress associated with deep cavity restoration and dental extractions, and pain associated with buccal and palatal injections and inferior alveolar nerve block.

ZAP Topical Anaesthetic Gel

- 3.11 The Committee noted that ZAP Topical Anaesthetic Gel is supplied in a 50 g jar with a one-touch dispenser allowing 0.2–0.3 mL of gel to be applied to the desired area using a cotton swab or fingertip.
- 3.12 The Committee noted that ZAP Topical Anaesthetic Gel is indicated to reduce the discomfort of local anaesthetic injected into the mandibular mucobuccal fold and maxillary anterior sites, and to minimise pain in oral mucosal tissue arising from needle punctures, deep scaling procedures, prosthetic adjustments, clamp or crown placement, removal of primary teeth and suture removal; and for the reduction of pharyngeal (gag) reflex associated with the placement of various dental materials into the oral cavity.
- 3.13 The Committee considered that if ZAP Topical Anaesthetic Gel was listed it would likely replace some of the lidocaine 2% gel and benzocaine 20% gel currently used. The Committee considered given that there are other suitable listed alternatives (lidocaine 2% gel and benzocaine 20% gel) for the use of topical anaesthesia that the unmet health need was likely to be low.
- 3.14 The Committee noted that no evidence regarding the efficacy and safety of ZAP Topical Anaesthetic Gel had been provided, and that none could be identified by the Committee. In addition, the Committee noted there was no available evidence regarding reapplication rates of ZAP gel compared to any other topical anaesthetics. The Committee therefore considered that it was uncertain whether ZAP gel would provide similar, worse or better effects when compared to other topical anaesthetic agents.

- 3.15 The Committee noted that Oraqix is a periodontal gel containing lidocaine (25 mg/g) and prilocaine (25 mg/g) supplied in dental cartridges in individual blister packs. The Committee noted that Oraqix can only be applied using a specific re-usable oraqix dispenser with a precision applicator tip.
- 3.16 The Committee noted that Oraqix is indicated in adults for localised anaesthesia in periodontal pockets for probing, scaling, and/or root-planing. The Committee noted that one 1.7 g cartridge of Oraqix is sufficient for one quadrant of dentition. Members considered that some patients may require anaesthesia to all four quadrants and could therefore require four cartridges in one sitting.
- 3.17 The Committee considered that Oraqix treatment would require DHB oral health providers to purchase specific Oraqix applicators, and that this would be an additional cost to the sector.
- 3.18 The Committee noted that the evidence for the efficacy of Oraqix compared with placebo for periodontal pocket anaesthesia prior to periodontal debridement comes from three randomised controlled trials.
- 3.19 The Committee noted the results of a randomised, double-blind, placebo-controlled clinical trial which investigated the efficacy and safety of Oraqix compared with placebo in 122 patients undergoing periodontal scaling or root planing ([Jeffcoat et al. J Periodontol. 2001;71:895-900](#)). The Committee noted that the median VAS pain score after scaling or planing was 7 mm in the Oraqix group and 17 mm in the placebo group (Hodges Lehmann-estimate of the treatment difference 8 mm; $P < 0.0005$), and that 90% of patients in the Oraqix group reported no pain or mild pain on a verbal rating scale (VRS) compared with 64% of patients in the placebo group ($P = 0.001$). The Committee noted that rescue anaesthesia was used by 11% of patients in the Oraqix group and 17% of patients in the placebo group.
- 3.20 The Committee noted the results of a randomised, double-blind, placebo controlled clinical trial which investigated the efficacy and safety of Oraqix compared with placebo in 130 patients undergoing periodontal debridement ([Donaldson et al. J Clin Periodontol. 2003;30:171-5](#)). The Committee noted that the median VAS pain score after debridement was 5 mm in the Oraqix group compared with 13 mm in the placebo group (Hodges Lehmann-estimate of the treatment difference 4 mm; $P = 0.015$), and that 78% of patients in the Oraqix group reported no pain or mild pain on a VRS compared with 76% in the placebo group. The Committee noted that rescue anaesthesia was needed for 6% of patients in the Oraqix group and 10% of patients in the placebo group.
- 3.21 The Committee noted the results of a randomised, double-blind, placebo controlled clinical trial which investigated the efficacy and safety of Oraqix compared with placebo in 85 pain-sensitive patients undergoing periodontal scaling or root planing ([Magnusson et al. J Periodontol. 2003;74:597-602](#)). The Committee noted that the median VAS pain score was 11 mm in the oraqix group compared with 27 mm in the placebo group (Hodges Lehmann-estimate of the treatment difference 10 mm; $P = 0.004$), and that 70% of patients in the Oraqix group reported no pain or mild pain on a VRS compared with 48% in the placebo group ($P = 0.003$). The Committee noted that rescue anaesthesia was needed for 5% of patients in the Oraqix group and 17% of patients in the placebo group.
- 3.22 The Committee noted that Oraqix was well tolerated and no safety concerns were identified in any of the three clinical trials comparing Oraqix with placebo.
- 3.23 The Committee noted a clinical study which investigated the efficacy of Oraqix compared with EMLA cream (with benzocaine 20% gel as a control) on pain experienced during palatal

needle prick ([Al-Melh & Andersson. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:e16-20](#)). The Committee noted that pain scores were significantly lower with EMLA cream and Oraqix compared with benzocaine 20% ($P < 0.05$). The Committee considered that the reduction in pain observed with EMLA cream and Oraqix were similar.

- 3.24 Members considered that based on the study by Al-Melh & Andersson (2000), EMLA cream was reported to have a better taste than Oraqix and benzocaine 20% gel; and could be expected to provide a similar health benefit to Oraqix at a much lower cost.
- 3.25 The Committee considered that the data from the Oraqix clinical trials indicated that up to 76% of patients receiving placebo experience no pain or only mild pain during periodontal debridement. The Committee considered that, based on this, the health need of patients undergoing periodontal debridement procedures is likely to be low and questioned whether there was a need for a local anaesthetic for periodontal debridement procedures.
- 3.26 The Committee considered that the Oraqix dispenser is designed for periodontal procedures to obviate the need for local anaesthetic injection but that it is not clear that this represents an unmet health need.
- 3.27 The Committee considered that the place of Oraqix to reduce pain for scaling and other periodontal procedures was uncertain. The Committee considered that if Oraqix was listed that this could represent a significant financial impact due to high cost of Oraqix without a quantifiable health benefit.

4 Calcipotriol with betamethasone foam spray for the treatment of psoriasis vulgaris

- 4.1 The Committee reviewed the application for calcipotriol 50 mcg/g with betamethasone 500 mcg/g foam spray, 60 g pack, in the treatment of psoriasis vulgaris.
- 4.2 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 4.3 The Committee recommended that calcipotriol/betamethasone foam spray be funded only if cost-neutral to the combined pharmaceutical budget compared to the currently funded calcipotriol/betamethasone gel, taking into account that patients may use more of the calcipotriol/betamethasone foam preparation and for longer periods compared to the calcipotriol/betamethasone gel.

Discussion

- 4.4 The Committee considered an application from Leo Pharma for calcipotriol with betamethasone foam spray for the treatment of psoriasis vulgaris. The Committee noted that this product contained a combination of calcipotriol, a vitamin D analogue, and betamethasone dipropionate, a potent topical corticosteroid.
- 4.5 The Committee noted that psoriasis affects 2-3% of the population and about 80% of psoriasis is of the vulgaris type. Members noted that there are many topical and systemic treatments currently funded for the management of psoriasis vulgaris, including the combination of calcipotriol with betamethasone in gel and ointment formulations.
- 4.6 The Committee noted that while psoriasis vulgaris was a chronic condition, patients generally

use topical treatments intermittently. Typically, patients start using a topical treatment during a flare, then cease use once the condition was under control and resume when flares recur. Members also noted that clinical practice was to advise patients with psoriasis not to use topical steroids continuously.

- 4.7 The Committee also noted that psoriasis was a difficult condition to manage and not all topical treatments are effective in individual patients; this results in patient dissatisfaction and the need to trial several different treatments.
- 4.8 The Committee noted that evidence for the foam formulation was from four pharmaceutical supplier-funded studies, namely:
- LEO 90100-7. Phase 2 comparing the new combination foam to individual components in the foam vehicle ([Lebwohl M, et al. J Clin Aesthet Dermatol. 2016;2:34–41](#))
 - LP0053-1001 (PSO-FAST). Phase 3 comparing the new combination foam, to foam vehicle ([Leonardi C, et al. J Drugs Dermatol. 2015;12:1468–77](#))
 - LP0053-1003 (PSO-ABLE). Phase 3 head to head trial comparing the new combination foam, with Daivobet gel ([Paul C, et al. J Eur Acad Dermatol Venereol. 2017;31:119–126](#))
 - Subgroup analysis of PSO-ABLE patients with moderate to severe psoriasis ([Paul C, et al. Am J Clin Dermatol. 2017;18:405–11](#)).
- 4.9 The Committee noted that in these studies a total of 749 patients were treated with the combination foam and 683 patients used a comparator; and that the results showed a consistent modified PASI75 of approximately 50% for the combination foam formulation, 34-40% for the combination gel, 34% for steroid-only in the foam vehicle, and 14% for calcipotriol-only in foam vehicle. Members noted the quicker onset of improvement for the combination foam versus the combination gel, which continued in the extension studies to 12 weeks; however, the Committee considered this was not clinically significant given psoriasis vulgaris was a chronic, incurable condition.
- 4.10 The Committee noted that in the PSO-ABLE study (Paul, et al.) patients used more foam than gel, although this may reflect patients stopping using the gel. Members noted that the mean total amount of combination foam used from baseline to week 4 was 98.6 grams, whereas the mean total amount of combination gel used from baseline to week 8 was 164.3 grams. Over 12 weeks, the amount of combination foam used was 236.4 grams, whereas the total amount of combination gel used was 193.1 grams.
- 4.11 The Committee considered the evidence to be of moderate strength and quality but noted that blinding was not possible due to the distinct physical properties of the different formulations. Members noted that the four pivotal trials were all company-sponsored but that the trials found similar levels of benefit, which the Committee considered indicative of some internal validity of the findings.
- 4.12 The Committee also noted the PSO-ABLE quality of life (QoL) study ([Griffiths CE, et al. Eur J Dermatol. 2018;28:356-363](#)) that looked at Dermatology Life Quality Index (DLQI), EuroQoL-5D-5L-PSO (EQ-5D), and Psoriasis QoL (PQoL-12) taken at baseline, weeks 4, 8 and 12. Members noted that significantly more combination foam patients achieved DLQI scores of 0/1 at week 4 (45.7% vs 32.4%; $p = 0.013$) and week 12 (60.5% vs 44.1%; $p = 0.003$) than combination gel patients. The combination foam significantly improved EQ-

5D utility index (0.09 vs 0.03; $p < 0.001$) and PQoL-12 scores (-2.23 vs -2.07; $p = 0.029$) from baseline to week 4 versus the combination gel. The Committee also noted that itch, itch-related sleep loss, and work impairment improved more with the combination foam than the gel.

- 4.13 The Committee considered psoriasis to have a significant impact on quality of life. Members noted that the evidence of QoL improvement was of moderate strength and quality, with a clinically relevant difference of a 10% improvement of PASI75 with the combination foam compared to the combination gel. The Committee noted this effect may be due to patient preference for the foam preparation.
- 4.14 The Committee considered, in summary, that while the combination foam had a faster response rate and improved efficacy over the combination gel, this may have been due to patients using more of the foam and increased adherence. Members noted that there were other ways of improving treatment adherence, as demonstrated in the following studies:
- [Svendsen MT, et al. Br J Dermatol. 2018 Apr 14](#) doi: 10.1111/bjd.16667. [Epub ahead of print]
 - [Caldarola G, et al. J Dermatolog Treat. 2017;28:772–5](#)
 - [Reich K, et al. Br J Dermatol. 2017;177:197–205.](#)
- 4.15 The Committee noted that use of patient-centric interventions, such as a smartphone application (Svendsen MT, et al), or an additional 20-minute individualised treatment educational session (Caldarola G, et al), or a comprehensive support programme to optimise treatment (Reich K, et al), all showed similar improvements in adherence and outcome between the combination gel and foam.
- 4.16 The Committee considered that the population group that would benefit most from the foam would be patients with mild to severe psoriasis vulgaris who do not require systemic therapy. Members were of the view that use of the combination foam would not delay progression to biologic therapy as patients requiring the latter were a different subgroup of the psoriasis vulgaris population.
- 4.17 The Committee considered that the key aspects of this funding application were a change in formulation, patient preference, adherence, and costs. Members considered that it was likely the combination foam preparation represented an improvement in the patient experience of using the product and that the foam may have greater suitability due to it being easier to use. However, the Committee expressed concerns about the potential flammability of the foam.
- 4.18 The Committee noted that if calcipotriol/betamethasone foam was to be funded, that there would still be a clinical need for other formulations (either combination or single ingredient products) in the management of psoriasis vulgaris as patient often prefer different formulations, depending on effectiveness and the body area affected. Members considered that at least half of patients currently using the calcipotriol/betamethasone gel or ointment might be switched to the combination foam and that a significant number of patients with psoriasis on other topical therapies may also switch to the calcipotriol/betamethasone foam spray. The Committee noted the cumulative effect of this would be an increase in overall patient numbers on combination treatments.
- 4.19 The Committee noted that calcipotriol/betamethasone foam was higher in price than the equivalent amount of combination gel, and considered that this may represent a premium being placed on product that is cosmetically preferable and easier to use. Members

acknowledged that the combination foam may be more effective, but that this may be due to patients using more of it and for a longer duration. The Committee considered that if the combination foam was to be funded, that PHARMAC would need to take into account this higher and longer use, compared to the combination gel, as well as a potential increase in the patient group using a combination product, and future generic competition for the combination gel.

- 4.20 The Committee noted an absence of long term, i.e. more than one year's, data for the calcipotriol/betamethasone combination foam but noted that there was over ten years' of real-world use of the combination ointment and gel formulations.

5 Abiraterone acetate for the treatment of high-risk metastatic hormone-naïve prostate cancer and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer

Application

- 5.1 The Committee reviewed an application for abiraterone acetate to be used in combination with prednisone and androgen deprivation therapy for the treatment of high-risk metastatic hormone-naïve prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC).
- 5.2 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 5.3 The Committee **recommended** that abiraterone acetate in combination with prednisone and androgen deprivation therapy be funded with low priority for the treatment of high-risk metastatic hormone naive prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) subject to the eligibility criteria for the LATITUDE trial.
- 5.4 The Committee **recommended** that abiraterone acetate for use in combination with prednisone and androgen deprivation therapy in a wider group of patients than those meeting the eligibility criteria for the LATITUDE trial be deferred until additional data regarding use in these settings is available.
- 5.5 The Committee **recommended** that the application for abiraterone acetate for use in combination with prednisone and androgen deprivation therapy for the treatment of high-risk mHNPC and newly diagnosed high-risk metastatic mHSPC be referred to the Cancer Treatment Subcommittee of PTAC for advice regarding the current use of, and benefit of ADT plus docetaxel in the treatment of prostate cancer; appropriate Special Authority criteria for abiraterone (including whether amendment to the current metastatic castration-resistant prostate cancer [mCRPC] criteria would be required); and the potential benefit of abiraterone in a wider group of prostate cancer patients who do not fit the LATITUDE trial eligibility criteria.

Discussion

- 5.6 The Committee noted that prostate cancer is one of the most commonly diagnosed malignancies in men in New Zealand with more than 3000 cases diagnosed annually, and

accounting for more than 600 deaths per year.

- 5.7 The Committee noted that the current standard of care for patients with metastatic prostate cancer in New Zealand is androgen deprivation therapy (ADT) in combination with docetaxel where patients are fit enough to receive chemotherapy, or ADT alone. The Committee noted that ADT can include surgical orchiectomy or medical orchiectomy with gonadotropin-releasing hormone agonists with or without anti-androgens.
- 5.8 The Committee noted a cohort study which reported that Māori men had poorer survival outcomes compared with non-Māori men in New Zealand ([Obertová et al. BJU Int. 2015;115:24-30](#)). The Committee noted that the study concluded this was likely due to differences in cancer detection and management, partly driven by socioeconomic deprivation.
- 5.9 The Committee noted that abiraterone acetate is converted in vivo to abiraterone which selectively inhibits 17 α -hydroxylase/C17,20-lyase (CYP17), an enzyme required for androgen biosynthesis in testicular, adrenal, and prostatic tissues.
- 5.10 The Committee noted that abiraterone acetate is used in combination with prednisone or prednisolone in order to compensate for abiraterone-induced reduction in serum cortisol, thereby reducing the incidence of mineralocorticoid-related adverse events associated with CYP17 inhibition.
- 5.11 The Committee noted that abiraterone acetate is indicated in combination with prednisone or prednisolone and ADT for the treatment of high-risk mHNPC and newly diagnosed high-risk mHSPC. The Committee considered that 'hormone naïve' was defined by the applicant as patients who have not previously received hormone therapy, or patients who have received up to 3 months of hormone therapy but have not become resistant. The Committee noted that this group can be considered a subset of the 'hormone- or castration-sensitive' group.
- 5.12 The Committee noted that abiraterone is also indicated for the treatment of patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, and for the treatment of patients with mCRPC who have received prior chemotherapy containing a taxane. The Committee noted that abiraterone has been funded for both taxane-naïve and taxane-pre-treated mCRPC patients since 2015.
- 5.13 The Committee noted that the recommended dose of abiraterone acetate for mHNPC or mHSPC is 1000 mg as a single-daily dose in combination with 5 mg prednisone or prednisolone, whereas mCRPC is recommended with 10 mg of corticosteroid.
- 5.14 The Committee noted that abiraterone acetate should be used with caution in patients with a history of cardiovascular disease, in patients with moderate or severe hepatic impairment, and in patients receiving drugs activated or metabolised by CYP2D6 or strong inhibitors and inducers of CYP3A4.
- 5.15 The Committee noted that the key clinical evidence to support the application for abiraterone acetate comes from the double-blind, placebo-controlled, phase 3 LATITUDE trial, which investigated the clinical benefit of ADT in combination with abiraterone acetate plus prednisone compared with ADT in combination with dual placebos in 1199 patients with newly diagnosed (≤ 3 months), high-risk, metastatic, castration-sensitive prostate cancer ([Fizazi et al. N Engl J Med. 2017;377:352-360](#)).

- 5.16 The Committee noted that to be considered 'high-risk' in the LATITUDE trial, patients were required to have two of the following high-risk factors: a Gleason score of eight or more, at least three bone lesions, or the presence of measurable visceral metastasis. The Committee considered that the definition of 'high-risk' was reasonable but not uniformly agreed upon by clinicians.
- 5.17 The Committee noted that patients were excluded from the LATITUDE trial if they had received previous chemotherapy, radiation therapy, or surgery for metastatic prostate cancer, with the exception of three months or less of ADT with luteinizing hormone-releasing hormone analogues or orchiectomy with or without concurrent first-generation androgen-receptor antagonists before baseline, or one course of palliative radiation or surgical therapy to treat symptoms associated with metastatic disease.
- 5.18 The Committee noted that after a median follow-up of 30.4 months at a planned interim analysis of LATITUDE, the median overall survival (OS) was not reached in the abiraterone acetate group compared with 34.7 months in the placebo group (HR 0.62; 95% CI, 0.51 to 0.76; $P < 0.001$). The Committee noted that the median radiographic progression-free survival (PFS) was 33.0 months in the abiraterone acetate group compared with 14.8 months in the placebo group (HR 0.47; 95% CI, 0.39 to 0.55; $P < 0.001$).
- 5.19 The Committee noted the results of the secondary efficacy endpoints of LATITUDE: median time to pain progression (not reached abiraterone acetate vs 16.6 months placebo; (HR 0.70; 95% CI 0.58 to 0.83; $P < 0.001$), median time to PSA progression (33.2 months vs 7.4 months; HR 0.30; 95% CI, 0.26 to 0.35; $P < 0.001$), median time to next symptomatic skeletal event (not reached vs not reached; HR 0.70; 95% CI, 0.54 to 0.92; $P = 0.009$), median time to chemotherapy (not reached vs 38.9 months; HR 0.44; 95% CI, 0.35 to 0.56; $P < 0.001$), and median time to subsequent prostate cancer therapy (not reached vs 21.6 months; HR 0.42; 95% CI 0.35 to 0.50; $P < 0.001$).
- 5.20 The Committee noted that, as a result of the findings at the time of the interim analysis, the LATITUDE trial was unblinded to allow for crossover from placebo to abiraterone acetate. Members considered that further analysis of the crossover population including details of demographics and analysis using a rank-preserving structural failure time model may be useful to help with interpretation of results where crossover had occurred.
- 5.21 The Committee noted that in LATITUDE, grade 3-4 mineralocorticoid-related adverse events occurred at a higher frequency in patients who received abiraterone acetate (hypertension: 20% abiraterone acetate vs 10% placebo; hypokalaemia: 10% abiraterone acetate vs 1% placebo).
- 5.22 The Committee noted the updated efficacy and safety data from the pre-planned second interim analysis of LATITUDE presented at the American Society of Clinical Oncology (ASCO) 2018 ([Fizazi et al. J Clin Oncol 36. 2018 \[suppl; abst 5023\]](#)). The Committee noted that after a median follow-up of 41.4 months, 60 of 70 patients in the placebo group who were continuing to receive treatment had crossed over to the abiraterone acetate group. The Committee noted that the median OS was not reached in the abiraterone acetate group compared with 36.7 months in the placebo group (HR 0.638; 95% CI, 0.538 to 0.758; $P < 0.0001$).
- 5.23 The Committee noted the results of the patient-reported outcome and health-related quality of life (HRQoL) analysis of the LATITUDE study ([Chi et al. Lancet Oncol. 2018;19:194-206](#)). The Committee noted that the median time to worst pain intensity was not reached in either

group (25th percentile: 11.07 months abiraterone acetate vs 5.62 months placebo; HR 0.63; 95% CI, 0.52 to 0.77; P<0.0001), that the median time to worst fatigue intensity was not reached in either group (25th percentile: 18.4 months vs 6.5 months HR 0.65; 95% CI 0.53 to 0.81; P=0.0001), and that the median time to deterioration of functional status was 12.9 months in the abiraterone acetate group compared with 8.3 months in the placebo group (HR 0.85; 95% CI 0.74 to 0.99; P=0.032). The Committee noted that patients in the abiraterone acetate group had better general health status scores and health utility compared with patients in the placebo groups, and that this was observed throughout the study.

- 5.24 The Committee noted that additional evidence for the use of abiraterone acetate for the treatment of prostate cancer is provided by the open-label, phase 2-3 STAMPEDE trial; a multi-arm, multi-stage, platform design trial, which investigated the efficacy of ADT in combination with additional agents (including zoledronic acid, docetaxel and celecoxib) in men with locally advanced or metastatic prostate cancer in the first-line setting (or ≤12 weeks of prior ADT).
- 5.25 The Committee noted that patients eligible for STAMPEDE had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumour stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng/mL) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment) ([James et al. N Engl J Med. 2017;377:338-351](#)).
- 5.26 The Committee noted an analysis of STAMPEDE which compared patients who received ADT alone (Arm A) and patients who received abiraterone acetate plus prednisolone in combination with ADT (Arm G) ([James et al. N Engl J Med. 2017;377:338-351](#)). The Committee noted the subgroup analysis of patients with metastatic disease which reported 150/500 deaths in the abiraterone acetate plus ADT group and 218/502 deaths in the ADT alone group (HR 0.61; 95% CI 0.49 to 0.75).
- 5.27 The Committee noted that 52% of patients in the STAMPEDE trial had metastatic disease and considered that this population was broader than that of the LATITUDE trial, as not all patients had high-risk disease and some patients had received previous treatment for their metastatic disease.
- 5.28 The Committee noted a second analysis of STAMPEDE which compared patients who received ADT in combination with docetaxel plus prednisolone (Arm C) and patients who received ADT in combination with abiraterone acetate plus prednisolone (Arm G) ([Sydes et al. Ann Oncol. 2018;29:1235-1248](#)). The Committee noted the subgroup analysis of patients with metastatic disease which reported 89/227 deaths in the abiraterone acetate group compared with 38/115 deaths in the docetaxel group (HR 1.13; 95% CI 0.77 to 1.66; P=0.528). The Committee noted that the incidence of adverse events was similar between the groups but was comprised of different toxicities in line with the known properties of the agents.
- 5.29 The Committee considered that as the study populations in STAMPEDE differed between the treatment arms direct comparison of outcomes was of limited value.
- 5.30 The Committee considered that a number of clinical trials have demonstrated a reduced risk of progression with docetaxel plus ADT compared with ADT alone in patients with mHSPC;

however, the Committee also considered that the addition of docetaxel to ADT results in increased toxicity and reduction in HRQoL compared with ADT alone.

- 5.31 The Committee noted a systematic review and meta-analysis presented at ASCO in 2018 which investigated the castration resistance-free survival (CFS) and toxicity of adding abiraterone acetate or docetaxel to ADT in five studies ([Helou et al. J Clin Oncol 36. 2018; no. 6 suppl:354-354](#)). The Committee noted that the study reported that the addition of abiraterone acetate and docetaxel to ADT increased CFS in men with hormone-sensitive prostate cancer, with a longer CFS noted for abiraterone acetate compared with docetaxel.
- 5.32 The Committee noted that guidelines from ASCO, EAU, ESMO, NCCN, and SEOM recommend first-line ADT in combination with docetaxel or ADT in combination with abiraterone acetate plus prednisone for patients with mHSPC who are fit enough to receive these regimens.
- 5.33 The Committee considered that the addition of abiraterone acetate and prednisone/prednisolone to ADT likely provides a benefit over ADT alone, but considered that there is currently insufficient evidence demonstrating a benefit compared with ADT in combination with docetaxel; which is likely the most appropriate comparator treatment in the first-line setting.
- 5.34 The Committee considered that the group with the most significant unmet health need among patients with high-risk mHNPC and newly diagnosed high-risk mHSPC are those who are not considered fit enough to receive docetaxel.
- 5.35 The Committee considered that the results of the LATITUDE trial support the use of abiraterone acetate plus prednisone in combination with ADT in the requested patient group. The Committee also considered that the results of STAMPEDE are consistent with abiraterone acetate benefiting a wider group of patients. This includes patients who have received prior treatment for their metastatic disease provided they remain hormone-sensitive, patients who do not have high-risk disease, and patients with locally advanced disease. However, the Committee considered there was a lack of robust evidence at this time to support the addition of abiraterone acetate in these settings and to indicate whether treatment with abiraterone earlier in the disease course would preclude its use in mCRPC.
- 5.36 The Committee considered that if funding for abiraterone acetate were to be extended to the requested population, additional monitoring would be required, including monthly blood pressure, serum potassium, and fluid retention monitoring; and three-monthly liver function testing. The Committee considered that this monitoring could have a significant impact on the health system and should be included in the economic assessment.
- 5.37 The Committee considered that if abiraterone acetate were to be funded, the uptake would likely be high due to the preference for an oral formation and a strong desire for patients to avoid surgical orchiectomy and chemotherapy. For these reasons, the Committee considered that an appropriate definition of the patient population eligible for funding in any access criteria would be important to limit fiscal risk.
- 5.38 The Committee noted that there are a large number of clinical trials investigating other agents such as enzalutamide, checkpoint inhibitors, and lutetium for the treatment of prostate cancer, particularly with a view for use in first-line settings.

6 Olaparib for the maintenance treatment of platinum-sensitive BRCA-mutated relapsed ovarian cancer

Application

- 6.1 The Committee reviewed a funding application from AstraZeneca for the use of olaparib for the treatment of BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high-grade serous features or a high-grade serous component.
- 6.2 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 6.3 The Committee **recommended** that olaparib be funded with a medium priority for the treatment of BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high grade serous features or a high-grade serous component subject to the Special Authority criteria proposed by CaTSoP at its April 2018 meeting but requested clarification from CaTSoP as to the appropriate definition of germline BRCA mutation to be used.

Discussion

- 6.4 The Committee noted that funding of olaparib for platinum-sensitive, BRCA mutated relapsed ovarian cancer had been previously considered by PTAC at its meeting in May 2017 where it had recommended deferring the application pending publication of the results of the SOLO2 study.
- 6.5 The Committee noted that CaTSoP had considered the application including the results of the SOLO2 study at its meeting in April 2018 and recommended funding with a high priority for patients with germline BRCA-mutated platinum-sensitive relapsed ovarian subject to the following Special Authority criteria:

Special Authority for Subsidy – Retail Pharmacy – Specialist

Initial – only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 12 months.

All of the following:

1. Patient has high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
2. There is documentation confirming germline *BRCA1* or *BRCA2* gene mutation; and
3. Patient has received at least two lines of previous treatment with platinum-based chemotherapy; and
4. Patient has platinum sensitive disease defined as disease progression occurring at least 6 months after the last dose of the penultimate line of platinum-based chemotherapy; and
5. Patient's disease must have achieved partial or complete response to treatment with the immediately preceding platinum-based regimen; and
6. Patient's disease has not progressed following prior treatment with olaparib; and
7. Treatment will be commenced within 8 weeks of the patient's last dose of immediately preceding platinum-based regimen; and
8. Treatment to be administered as maintenance treatment; and
9. Treatment not to be administered in combination with other chemotherapy.

Renewal – only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 12 months.

All of the following:

1. Treatment remains clinically appropriate and patient is benefitting from treatment; and
2. No evidence of progressive disease; and
3. Treatment to be administered as maintenance treatment; and
4. Treatment not to be administered in combination with other chemotherapy.

Note: *high grade serous includes tumours with high-grade serous features or a high-grade serous component

- 6.6 The Committee noted that when reviewing the minutes of the April 2018 CaTSoP meeting, CaTSoP requested that the application for olaparib including the results of the SOLO-2 study be reviewed by PTAC at a future meeting along with additional information regarding quality of life in the requested patient population.
- 6.7 The Committee noted that the health need of patient with BRCA mutated platinum-sensitive ovarian cancer was documented in previous PTAC and CaTSoP minutes regarding consideration of funding for olaparib in this population.
- 6.8 The Committee noted that the natural history of ovarian cancer was for sequential rounds of platinum chemotherapy and/or surgery following diagnosis with reducing intervals between treatment and relapses.
- 6.9 The Committee noted that the SOLO-2 was a randomised, placebo-controlled, double-blind Phase 3 trial in 295 patients with histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancers, who had a predicted deleterious or suspected deleterious BRCA1/2 mutation, assigned 2:1 to olaparib (300 mg in two 150 mg tablets, twice daily) or matching placebo tablets (Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18:1274-84).
- 6.10 The Committee noted that patients eligible for SOLO-2 had received two or more prior platinum-based chemotherapy regimens and were in objective response (either complete response or partial response according to modified RECIST version 1.1 or CA-125 levels to their most recent regimen), were platinum-sensitive disease following their penultimate line of chemotherapy, and had a predicted deleterious (class 5) or suspected deleterious (class 4) BRCA1/2 mutation.
- 6.11 The Committee noted that investigator-assessed progression-free survival (PFS), the primary endpoint, was 19.1 months [95% CI 16.3–25.7] in the olaparib arm and 5.5 months [5.2–5.8] in the placebo arm (HR 0.30, 95% CI 0.22–0.41, $p < 0.0001$).
- 6.12 The Committee considered that there was likely a durable increase in PFS during the study period and that currently available evidence for other PARP inhibitors in germline BRCA mutated ovarian cancer indicated this appeared to be a consistent signal.
- 6.13 The Committee noted health-related quality of life and patient-centred outcomes from SOLO2 reported by Freidlander et al *Lancet Oncol* 2018; 19: 1126–34 which included the duration of good quality of life (defined as quality adjusted time without significant symptoms of toxicity [Q-TWiST] and quality-adjusted progression-free survival [QAPFS]). The Committee considered that Q-TWiST attempted to balance the PFS with symptom measures, however, this approach is not commonly used and there are some criticisms of this in the literature. Specifically, Q-TWiST is not a comprehensive measure of quality of life (capturing only grade 3 and 4 adverse events), the utility selection appeared arbitrary, and there appeared to be significant variability of methodology across trials where it had been used.

- 6.14 The Committee considered that quality of life data from SOLO2 indicated a comparable result between both arms while on treatment, but it was noted that standard quality of life measures are censored following disease progression, creating a lack of information regarding quality of life from progression until the time the next treatment line commenced, which is a clinically relevant time period in ovarian cancer. The Committee considered that for this reason quality of life for patients taking olaparib was likely overestimated however, likely remained comparable to placebo.
- 6.15 The Committee noted that results of SOLO1 had recently been published ([Moore et al NEJM 2018; DOI: 10.1056/NEJMoa1810858](#)) a randomised, double-blind, placebo-controlled phase III trial of olaparib (300mg twice daily) as maintenance therapy in patients with newly diagnosed advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with a BRCA1/2 mutation who had a complete or partial clinical response after first-line platinum-based chemotherapy. The Committee considered that PFS results at 51% data maturity indicated that there was likely overlap with use of this agent after later lines of platinum chemotherapy and did not indicate a significantly reduced quality of life.
- 6.16 Overall, the Committee considered that while the number of treatment lines for ovarian cancer patients was unlikely to change there was likely a benefit from longer durations between lines of chemotherapy treatment without a reduction in quality of life for patients with pathologic germline BRCA mutated relapsed ovarian cancer patients from the use of olaparib.
- 6.17 The Committee noted that the Special Authority criteria for olaparib recommended by CaTSoP at its April 2018 meeting did not specify the type of germline BRCA mutation meaning if implemented patients with any germline BRCA mutation would be eligible. The Committee noted the categorisation of BRCA mutations by the ENIGMA Consortium was cited in the PBAC assessment of olaparib and also noted by CaTSoP in previous minutes regarding olaparib.
- 6.18 The Committee noted that there was a lack of data for germline BRCA mutation in Māori and Pacific populations, leading to potential bias against these populations in PARP inhibitor eligibility. The Committee also noted that only patients with ENIGMA class 4 (likely pathogenic) or 5 (definitely pathogenic) BRCA1/2 mutations were included in SOLO2.
- 6.19 The Committee queried whether restriction to definitively pathological mutation types would be appropriate in a New Zealand setting. The Committee requested further clarification from CaTSoP with regards to the appropriate definition of BRCA mutation in the Special Authority criteria for olaparib noting that consideration should be given to whether this may disenfranchise minorities who may be less likely to have mutations classified as pathological in databases primarily due to limited data points.

7 Pembrolizumab for the treatment of metastatic non-small cell lung cancer in combination with chemotherapy

Application

- 7.1 The Committee reviewed an application from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab in combination with chemotherapy for first line treatment of metastatic non-small cell lung cancer (NSCLC).
- 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 pembrolizumab in combination with chemotherapy for the first line treatment of metastatic NSCLC with no EGFR or ALK genomic tumour aberrations be funded with a medium priority.
- 7.4 The Committee **recommended** that the application be referred to the Cancer Treatment Subcommittee of PTAC (CaTSoP) for advice regarding the lung cancer treatment landscape, potential placement of pembrolizumab combination regimens in the treatment paradigm, appropriate Special Authority criteria, and further consideration of use of PD-L1 expression as a biomarker.

Discussion

- 7.5 The Committee noted that funding applications for immune checkpoint inhibitors for the treatment of advanced NSCLC have been previously considered by PTAC and CaTSoP on a number of occasions including: atezolizumab, pembrolizumab and nivolumab in second and third line settings; and noted that PTAC had recommended all be funded with a low priority.
- 7.6 The Committee noted that pembrolizumab as monotherapy as a first-line treatment where tumours express PD-L1 at a level of $\geq 50\%$ had previously been considered by PTAC on a number of occasions. The Committee noted that PTAC had deferred making a recommendation regarding the funding of pembrolizumab as monotherapy as a first-line treatment of advanced PD-L1 positive NSCLC pending further data to support the use of pembrolizumab in this patient group. The Committee noted that additional information had been provided by the supplier, however, timing of receipt had meant this was not able to be considered at the current meeting.
- 7.7 The Committee noted that there was a significant unmet health need for lung cancer patients in New Zealand who had poor survival with currently funded treatments, that the majority of patients present with advanced disease, and that lung cancer rates are consistently higher for Māori compared with non-Māori.
- 7.8 The Committee noted that the current application for pembrolizumab in combination with chemotherapy is for use as a first-line treatment for metastatic NSCLC irrespective of PD-L1 expression.

Evidence

- 7.9 The Committee noted the primary evidence for the use of pembrolizumab in combination with chemotherapy as a first-line treatment for metastatic NSCLC comes from KEYNOTE-21G and KEYNOTE-189 in non-squamous histology and KEYNOTE-407 in squamous histology.

Non-Squamous NSCLC

- 7.10 The Committee noted KEYNOTE-021 is a randomized, open-label, phase 2 multicohort study (Langer et al. Lancet Oncol. 2016;17:1497-1508) and that cohort G investigated pemetrexed/carboplatin with or without pembrolizumab in 123 patients with previously untreated, stage IIIB or IV, non-squamous NSCLC without targetable EGFR or mutations.

- 7.11 The Committee noted that in KEYNOTE-021G treatment with pembrolizumab continued for 2 years, maintenance pemetrexed was permitted in both groups, and eligible patients with radiologic progression in the control arm could cross over to pembrolizumab monotherapy.
- 7.12 The Committee noted that after a median follow-up of 23.9 months, overall response rate, the primary endpoint, was 56.7% in the pembrolizumab arm and 30.2% in the control arm (estimated difference, 26.4%; 95% CI 8.9%–42.4%; P=0.0016) (Gentzler et al. ASCO 2018 abstract 9026 and Borghaei et al 2018 DOI [10.1016/j.jtho.2018.08.004](https://doi.org/10.1016/j.jtho.2018.08.004)).
- 7.13 The Committee noted that progression-free survival (PFS) was reported as 24.0 months in the pembrolizumab arm and 9.3 months in the control arm (HR 0.53 ,95% CI 0.33-0.86, p=0.0049); and median OS was not reached (NR) in the pembrolizumab arm (95% CI, 24.5 to NR months) and 21.1 months (95% CI, 14.9 to NR months) in the control arm (HR for OS 0.56, 95% CI, 0.32-0.95; p=0.0151).
- 7.14 The Committee noted that data from cohorts A, B, D and H has been published but it appears that data for others remain unpublished. The Committee noted that based on the results from cohort G the study was extended to KEYNOTE-189.
- 7.15 The Committee noted KEYNOTE-189 is a randomised double-blind phase 3 trial of pembrolizumab (200 mg Q3W up to a total of 35 cycles) or saline placebo plus platinum (Q3W for 4 cycles) and pemetrexed (Q3W) in 616 patients with metastatic non-squamous NSCLC without EGFR or ALK mutations and who had received no previous treatment for metastatic disease ([Gandhi et al. NEJM. 2018; 378:2078-2092](#)).
- 7.16 The Committee noted that participants were stratified according to PD-L1 expression (tumour proportion score, ≥1% vs. <1%), choice of platinum-based treatment and smoking history.
- 7.17 The Committee noted that crossover to pembrolizumab monotherapy was permitted among the patients in the control arm who had verified disease progression. The Committee noted that treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent; and if toxicity was clearly attributed to one agent, that drug alone could be discontinued.
- 7.18 The Committee noted that exclusion criteria included ECOG greater than 1, symptomatic CNS metastases, history of non-infectious pneumonitis which required glucocorticoids, active autoimmune disease or systemic immunosuppressive treatment and more than 30Gy of radiotherapy to the lung in the previous 6 months.
- 7.19 The Committee noted that after a median follow-up of 10.5 months, the median overall survival (OS) was not reached in the pembrolizumab arm and was 11.3 months (95% CI, 8.7 to 15.1) in the control arm (HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001).
- 7.20 The Committee noted that the estimated rate of OS at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab arm versus 49.4% (95% CI, 42.1 to 56.2) in the control arm (HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001).
- 7.21 The Committee noted that median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab arm and 4.9 months (95% CI, 4.7 to 5.5) in the control arm (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001).
- 7.22 The Committee noted that the response rate was 47.6% for the pembrolizumab arm and 18.9% for the control arm. The Committee noted that nearly all responses in the

pembrolizumab arm were partial responses (193 partial responses; 2 complete responses) and benefit in the pembrolizumab arm was observed in all subgroups analysed including those with PD-L1 tumour proportion score of <1%. The Committee considered that there did appear to be a stratification effect from PD-L1 expression.

- 7.23 The Committee noted that KEYNOTE-407 is a randomized double-blind phase 3 trial of carboplatin-paclitaxel/nab paclitaxel with or without pembrolizumab (200mg up to 35 cycles) in 559 patients with untreated metastatic (stage IV) squamous NSCLC ([Paz-Ares et al. NEJM 2018;379:2040-2051](#)). The Committee noted that nab-paclitaxel is registered but not currently funded for use in New Zealand.
- 7.24 The Committee noted that patients were stratified according to PD-L1 expression (tumour proportion score $\geq 1\%$ vs. $< 1\%$; choice of taxane (paclitaxel vs. nab-paclitaxel), and geographic region of enrolment (East Asia vs. the rest of the world).
- 7.25 The Committee noted that following centrally confirmed radiologic progression, patients in the control arm were eligible to cross over to receive pembrolizumab monotherapy; and patients could continue open-label pembrolizumab monotherapy despite radiographically confirmed disease progression.
- 7.26 The Committee noted that after a median follow-up of 7.8 months (range 0.1-19.1), the median OS was 15.9 months in the pembrolizumab arm and 11.3 months in the control arm (HR 0.64; 95% CI, 0.49 to 0.85; $P < 0.001$); and the median PFS was 6.4 months in the pembrolizumab arm and 4.8 months in the control arm (HR 0.56; 95% CI, 0.45 to 0.70; $P < 0.001$).
- 7.27 The Committee noted that there did not appear to be any head to head trials comparing pembrolizumab monotherapy with pembrolizumab in combination with chemotherapy for previously untreated advanced NSCLC.
- 7.28 The Committee noted an indirect treatment comparison provided by the supplier in metastatic non-squamous NSCLC with strongly positive PD-L1 (TPS $\geq 50\%$) using results from KEYNOTE-189 and 024.
- 7.29 The Committee noted PTAC had previously reviewed evidence for the use of pembrolizumab as monotherapy as a first-line treatment for 305 patients with advanced NSCLC with PD-L1 expression $\geq 50\%$ and no EGFR or ALK mutations from randomized, open-label, phase 3 KEYNOTE-024 trial (Reck et al. NEJM 2016;375:1823-33).
- 7.30 The Committee considered that the supplier's indirect comparison indicated there may be a modest benefit from combination treatment over chemotherapy alone in this population. However, this represented only a subgroup of the patients requested for funding and as with any indirect comparison there were difficulties with interpretation.
- 7.31 Members considered this analysis appeared to be the rationale for the suggested algorithm that patients with PD-L1 expression of 50% or greater be treated with the combination regimen and a monotherapy regimen be used for other patients.
- 7.32 The Committee noted KEYNOTE-042 is a randomised phase 3 study investigating first-line chemotherapy (paclitaxel plus carboplatin or pemetrexed plus carboplatin) or pembrolizumab monotherapy in 1,274 people with locally advanced or metastatic squamous or non-squamous NSCLC without EGFR or ALK mutations and PD-L1 expression of 1% or more. The Committee noted results from this study presented in abstract form at ASCO 2018

(Lopes et al JCO 2018;36(suppl; abstr LBA4)).

- 7.33 The Committee noted that after a median follow-up of 12.8 months, median OS was reported in the pembrolizumab and chemotherapy arms respectively as follows: 16.7 vs 12.1 months for PD-L1 >1% (HR 0.80,0.71-0.93); 17.7 vs 13.0 months in PD-L1 >20% (HR 0.77, 0.64-0.92); and 20.0 vs 12.1 months for PD-L1 >50% (HR 0.69, 0.56-0.85).
- 7.34 The Committee considered that issues regarding the practicalities, reliability and potential inequity of PD-L1 expression testing to determine eligibility criteria described in previous PTAC and CaTSOP minutes regarding pembrolizumab for NSCLC remained relevant, however members considered there did appear to be a predictive value from high PD-L1 expression in NSCLC and response to pembrolizumab.
- 7.35 The Committee considered that there was emerging evidence for the use of other biomarkers, such as tumour mutation burden, and further information regarding the use and utility of biomarkers for targeting immune checkpoint inhibitors would be of interest.
- 7.36 The Committee considered that there was a different adverse event profile for chemotherapy than with immune checkpoint inhibitors alone, in that the toxicity profile of chemotherapy would appear within weeks whereas immune checkpoint inhibitor adverse events, particularly immune-mediated side-effects, emerges later at around 3 months. The Committee noted that the significant health sector resource required to manage patients with immune-mediated side effects had been discussed in previous minutes regarding immune checkpoint inhibitor agents.
- 7.37 The Committee considered that across the published evidence there appeared to be a consistent signal for a modest survival benefit from use of pembrolizumab in combination with chemotherapy in the first-line treatment of advanced NSCLC. However, considered the high price sought by the supplier was adversely affecting the cost-effectiveness of pembrolizumab.
- 7.38 Members considered that, based on currently available evidence, first line chemotherapy combination regimens for patients without EGFR mutations would be platinum and pemetrexed for non-squamous NSCLC and carboplatin and paclitaxel for squamous NSCLC; which differed to the current squamous platinum and gemcitabine regimen. Members noted that patients with EGFR mutations would continue to receive TKI agents as first-line treatment.
- 7.39 The Committee considered that the evidence for use of immune checkpoint inhibitors was rapidly advancing and noted that there was a large number of ongoing studies for the use of various immune checkpoint inhibitors, many in combination with various chemotherapy agents, in late stage clinical trial for the first-line treatment of advanced NSCLC. The Committee considered that it would be of value to compare the relative benefits of these treatment regimens when considering potential future treatment paradigms for advanced NSCLC.

8 Nivolumab for the treatment of relapsed clear cell renal cell carcinoma

Application

- 8.1 The Committee reviewed the application for nivolumab for the second-line treatment of relapsed clear cell renal cell carcinoma (RCC) following prior angiogenic therapy.

- 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 nivolumab be funded with a low priority for the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy subject to Special Authority criteria in line with published evidence and to be determined based on further advice from the Cancer Treatment Subcommittee of PTAC (CaTSoP).

Discussion

- 8.4 The Committee noted that CaTSoP reviewed a clinician application for nivolumab for the treatment of relapsed clear cell RCC at its meeting in August 2017 and had recommended funding with medium priority.
- 8.5 The Committee noted that at its February 2018 meeting PTAC had reviewed the August 2017 CaTSoP minute and requested to review the clinical evidence in relation to nivolumab for this indication at a future meeting.
- 8.6 The Committee noted that in 2012 the New Zealand Cancer Registry data recorded 897 registrations for cancers of the kidney and 168 deaths, clear cell RCC is around 85% of renal cancers, about 30% of patients present with advanced disease, and that mortality rates are higher in Māori compared with non- Māori.
- 8.7 The Committee noted that the VEGF tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib are currently funded as first-line agents for the treatment of clear cell RCC and there are currently no funded second-line treatment options for patients with disease refractory to sunitinib or pazopanib.
- 8.8 The Committee noted that the key clinical evidence for the use of nivolumab in the second-line treatment of advanced RCC comes from CHECKMATE-025, a randomised, open-label, phase 3 study of nivolumab (3mg/kg IV Q2W) in comparison with everolimus (10mg orally OD) in 821 patients with metastatic clear-cell RCC who had received previous antiangiogenic therapy. (Motzer et al. N Engl J Med. 2015;373:1803–13).
- 8.9 The Committee noted that eligibility criteria included no more than three previous regimens of systemic therapy and that the majority of participants (72%) had received one line of prior angiogenic therapy.
- 8.10 The Committee noted that after a minimum follow-up of 14 months, a 5.4 month gain in overall survival, the primary end-point, was reported: 25.0 months (95% CI, 21.8-not estimable) with nivolumab and 19.6 months (95% CI, 17.6-23.1) with everolimus (hazard ratio (HR) for death, 0.73; 98.5% CI, 0.57-0.93; P=0.002).
- 8.11 The Committee considered that no difference in progression-free survival was demonstrated, very few complete responses were achieved, and a median duration of response in both arms was around 1 year.
- 8.12 The Committee noted that 55% of patients in the nivolumab arm received subsequent treatment (everolimus, axitinib, pazopanib) and 63% in the everolimus arm (axitinib, pazopanib, sorafenib); and that 7 patients in everolimus arm received a subsequent anti-PD1 therapy. The Committee noted that 44% and 46% of patients in the nivolumab and

everolimus arms respectively continued treatment after disease progression as the investigator judged clinical benefit despite progression. The Committee considered that given the levels of crossover in both arms there was likely minimal impact of confounding from this, however, given the open-label trial design there was a high risk of patient performance bias, particularly in patient management decisions and in reporting health-related quality of life.

- 8.13 The Committee noted that an update of CHECKMATE-025 had been presented in abstract form at the 16th International Kidney Cancer Symposium in November 2017 reporting after a median follow-up of 24 months in the nivolumab arm, median OS of 25.8 months compared to 19.7 months for nivolumab and everolimus respectively (HR 0.74, $p=0.0005$ without reported confidence intervals).
- 8.14 The Committee noted health-related quality of life (HR-QoL) data from CHECKMATE-025 (Cella et al. Lancet Oncol 2016;17:994-1003) and considered that, whilst there appeared to be clinically important improvement in HR-QoL for patients treated with nivolumab using the FKSI-DRS tool, the magnitude of this benefit was difficult to ascertain; and the proportion of patients who had clinically meaningful HR-QoL improvement did not differ between the groups assessed with EQ-5D scores.
- 8.15 The Committee noted that longer term data from phase I and II studies of nivolumab in RCC were reporting 3 and 5 year OS rates for patients who had prior TKI treatment of around 70%.
- 8.16 The Committee considered that available evidence indicated there did not appear to be an association between PD-L1 expression, response to PD1 inhibition and survival in RCC, and that safety signals appeared to be comparable to the use of immune checkpoint inhibitors in other settings in that adverse events are relatively common and could be severe.
- 8.17 The Committee noted that everolimus was not a funded treatment for RCC in New Zealand and therefore considered that comparison of the magnitude of benefit patients would receive was uncertain, there likely was a survival benefit from nivolumab as a second-line RCC treatment
- 8.18 The Committee considered that the cost-effectiveness of nivolumab was adversely affected by the relatively high current pricing, and that any benefit should also be balanced with the impact of adverse events from immune checkpoint inhibition which could be significant and represent a significant burden to the health system. The Committee also noted that administration of nivolumab as a two-weekly infusion regimen would have an impact for DHB infusion services.
- 8.19 The Committee noted that there appear to be a number of ongoing trials for the use of checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab and avelumab) in combination with various other agents such as carbozantinib, axitinib and bevacizumab for the first-line treatment of advanced RCC.

9 Denosumab for the treatment of hypercalcaemia of malignancy or malignant bone disease in patients with severe renal impairment

Application

- 9.1 The Committee reviewed a clinician application for the listing of denosumab for the treatment of hypercalcaemia of malignancy or malignant bone disease in patients with multiple

myeloma who have severe renal impairment (creatinine clearance <30 mL/min).

- 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 the application for denosumab for the treatment of hypercalcaemia of malignancy or malignant bone disease in patients with severe renal impairment (creatinine clearance <30 mL/min) be declined based on both a low health need given the availability of funded treatment alternatives (i.e. intravenous hydration, diuretics and pamidronate), and concerns about the appropriate dosing of denosumab in this setting and associated risks of hypocalcaemia.

- 9.4 The Committee **recommended** that denosumab for the treatment of hypercalcaemia of malignancy in patients with severe renal impairment (creatinine clearance <30 mL/min) who are refractory to bisphosphonates be listed with a low priority subject to the following Special Authority criteria:

Initial application – only from a haematologist, oncologist, or palliative care specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:

1. Patient has hypercalcaemia of malignancy as defined by serum calcium above the Upper Limit of Normal; and
2. Patient has severe renal impairment defined as a creatinine clearance of <30 mL/min; and
3. Patient is refractory to treatment with bisphosphonates, defined by serum calcium levels corrected for albumin having not decreased below or equal to 2.90 mmol/L within 7 to 30 days of treatment with intravenous bisphosphonates.

Discussion

- 9.5 The Committee noted that hypercalcaemia is a common metabolic complication of malignancy that can occur as a result of either humoral mechanisms e.g. excessive production of parathyroid hormone-related protein or tumour production of 1,25-dihydroxyvitamin D, or osteolytic metastases. The Committee noted that the symptoms of hypercalcaemia include renal, gastrointestinal, neurological, musculoskeletal, and cardiovascular effects that range from mild (e.g. mild constipation) to severe (e.g. acute renal failure, coma, or death).

- 9.6 The Committee considered that it had seen no robust evidence about the effect of hypercalcaemia of malignancy on quality of life, although it was noted that the conditions is associated with a poor prognosis and significant morbidity.

- 9.7 The Committee considered that while patients with multiple myeloma are at particularly high risk of developing hypercalcaemia and renal impairment; that patients with hypercalcaemia or bone disease due to any malignancy have a similar health need and would receive the same level of benefit from treatment with denosumab. The Committee therefore considered that the application for denosumab should be considered for the treatment of hypercalcaemia or malignant bone disease due to any malignancy in patients with and severe renal impairment (creatinine clearance <30 mL/min) rather than in the setting of multiple myeloma alone.

- 9.8 The Committee noted data from a retrospective analysis of 569,000 patients treated at oncology outpatient sites in the United States which reported that approximately 2% of all patients with cancer experienced hypercalcaemia, and that 19.4% of these patients had renal impairment based on an estimated glomerular filtration rate <30 mL/min ([Gastanaga et al.](#)

[Cancer Med. 2016;5:2091-2100](#)). The Committee noted that using data from this study, PHARMAC staff have estimated that approximately 200 patients with per year would develop hypercalcaemia of malignancy with concurrent renal impairment. The Committee considered that this estimate may be high, as the source data included all patients who developed any grade hypercalcaemia, and it may only be patients with symptomatic or severe hypercalcaemia that require treatment.

- 9.9 The Committee noted that the aim of treatment of hypercalcaemia of malignancy is two-fold: acute treatment with intravenous hydration and diuretics rapidly lowers serum calcium levels, and treatment using bisphosphonates prevents recurrence and further deterioration of bone integrity by inhibiting osteoclast activity.
- 9.10 The Committee noted that the currently funded bisphosphonates used for the treatment of hypercalcaemia of malignancy are pamidronate disodium and zoledronic acid. The Committee noted that these agents are excreted via the kidneys and are contraindicated in patients with renal impairment (creatinine clearance <30-35 mL/min).
- 9.11 The Committee noted that denosumab is a fully human IgG2 monoclonal antibody that binds to RANKL, a transmembrane or soluble protein essential for osteoclast function.
- 9.12 The Committee noted that denosumab is registered in New Zealand for the treatment of osteoporosis in postmenopausal women administered as a single subcutaneous injection of 60 mg once every 6 months. The Committee considered that denosumab for the treatment of hypercalcaemia or malignant bone disease would be off-label use.
- 9.13 The Committee noted that denosumab is metabolised and eliminated via the immunoglobulin clearance pathway. The Committee considered that no dose adjustment of denosumab is recommended in patients with renal impairment, but that patients with severe renal impairment seem to be at greater risk of developing hypocalcaemia.
- 9.14 The Committee noted the results of a 16-week, open-label, single-dose clinical study which evaluated the pharmacokinetics and pharmacodynamics of a 60 mg dose of denosumab in 55 subjects with renal function ranging from normal to dialysis-dependent kidney failure ([Block et al. J Bone Miner Res. 2012;27:1471-9](#)). The Committee noted that within this study, renal function did not have a significant effect on denosumab pharmacokinetics or pharmacodynamics; however, it was noted the incidence of adverse events increased with increasing renal compromise, and that two patients with severe chronic kidney disease experienced hypocalcaemia that was considered serious.
- 9.15 The Committee considered that the primary evidence for the efficacy of denosumab for the treatment of hypercalcaemia of malignancy is provided by an open-label, single-arm, phase 2 clinical trial which investigated the efficacy and safety of denosumab for the treatment of hypercalcaemia of malignancy in 33 heavily pre-treated bisphosphonate-refractory patients with mixed renal function ([Hu et al. J Clin Endocrinol Metab. 2014;99:3144-52](#)). The Committee noted that patients were considered bisphosphonate-refractory if their serum calcium levels corrected for albumin (CSC) had not decreased below or equal to 11.5 mg/dL within 7 to 30 days of treatment with intravenous bisphosphonates. The Committee noted that, by day 10, 64% of patients reached a CSC \leq 11.5 mg/dL and 36% of patients achieved a CSC \leq 10.8 mg/dL (considered a completed response). The Committee noted that patients with impaired renal function (creatinine clearance <60 mL/min) responded to treatment in similar proportions to those with normal renal function (55% vs 59%). The Committee noted that at the time of the primary analysis, 31 of 33 patients had discontinued treatment (28 had

died), and 2 patients had reported non-symptomatic episodes of hypocalcaemia.

- 9.16 The Committee considered that there had been two responses published to the study conducted by Hue et al (2014) which raised concerns regarding the safety of the denosumab dosage and schedule used within the study (120 mg denosumab on days 1, 8, 15, and 29, and then every 4 weeks), particularly for patients with renal impairment ([Tsuda et al. J Natl Cancer Inst. 2014;106:dju137](#). [Adhikaree et al. J Natl Cancer Inst. 2015;107:dju509](#)). The Committee noted that the primary concern was in regards to the increased risk for severe hypocalcaemia; and that the authors recommended waiting at least 3 weeks between doses of denosumab, reducing the dose of denosumab in cases of substantial renal dysfunction, and ensuring calcium levels are regularly monitored.
- 9.17 The Committee considered that the evidence for the use of denosumab for the treatment of hypercalcaemia of malignancy in patients with renal impairment is limited to a case series of four patients with multiple myeloma ([Cicci et al. Clin Lymphoma Myeloma Leuk. 2014;14:e207-11](#)). The Committee noted that one patient received a fixed 60 mg dose of denosumab, and subsequently developed persistent hypocalcaemia requiring intravenous and oral calcium and vitamin D replacement therapy. The Committee noted that the remaining three patients received 0.3 mg/kg denosumab; these patients all experienced an initial correction of calcium levels, two went on to develop mild hypocalcaemia which normalized with time and one patient was subsequently deemed unresponsive to therapy.
- 9.18 The Committee noted the results of a double-blind, double-dummy, randomized, phase 3 clinical trial which compared denosumab with zoledronic acid for delaying or preventing skeletal-related events (SRE) in 886 patients with advanced cancer and bone metastases or myeloma ([Henry et al. J Clin Oncol. 2011;29:1125-32](#)). The Committee noted that within the study, treatment with denosumab was found to be non-inferior to zoledronic acid in delaying time to first on-study SRE. The Committee noted that hypocalcaemia occurred in 10.8% of patients who received denosumab and 5.8% of patients who receiving zoledronic acid; and that in patients with a creatinine clearance of <60 mL/min, renal adverse events occurred in 21.6% of patients receiving zoledronic acid and 11.3% receiving denosumab.
- 9.19 The Committee considered that the appropriate dosing regimen for denosumab for the treatment of hypercalcaemia of malignancy or malignant bone disease in patients with severe renal impairment (creatinine clearance <30 mL/min) remains unclear; and that clinical data indicates that there is a risk of developing hypocalcaemia with doses ≥60 mg. The Committee considered that a dose of 0.3 mg/kg, as used in Cici et al. (2014), may be appropriate in this patient group. Members noted that denosumab is provided as a 60 mg pre-filled syringe, which may complicate the use of an alternative dosing regimen such as weight-based dosing.
- 9.20 Members considered that, despite being contraindicated in patients with renal impairment, bisphosphonates are still used in this population where the benefits outweigh the risks. Members also considered that treatment of hypercalcaemia with bisphosphonates often improves renal function, as renal function can be negatively affected by elevated serum calcium levels. Members therefore considered that there may not be an unmet need for an alternative agent for the treatment of hypercalcaemia or malignant bone disease in patients with severe renal impairment (creatinine clearance <30 ml/min); however, the Committee considered that there may be an unmet health need for an alternative agent in patients with hypercalcaemia of malignancy who are refractory to treatment with bisphosphonates. The Committee considered that the evidence provided by Hu et al (2014) supports the use of denosumab in this population.

10 Evolocumab for the treatment of high-risk hypercholesterolaemia (homozygous and heterozygous familial hypercholesterolaemia)

Application

- 10.1 The Committee reviewed the application for evolocumab for use in the treatment of familial hypercholesterolaemia (FH), specifically homozygous and heterozygous familial hypercholesterolaemia (HoFH and HeFH).
- 10.2 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

- 10.3 The Committee **recommended** that the application to fund evolocumab for the treatment of high-risk hypercholesterolaemia (heterozygous familial hypercholesterolaemia) be declined.

Discussion

- 10.4 The Committee considered that people with HeFH and HoFH had a high health need and that the health need is higher in HoFH, as there is a high risk of coronary heart disease and premature cardiovascular events associated with HoFH.
- 10.5 The Committee noted that HeFH is defined clinically, using the Dutch Lipid Clinic or modified UK test, or by genetic testing. Members considered it was likely to be under-diagnosed in New Zealand Muir et al. (NZMJ 2010 123:1326, 97-102), noting that up to 20% of HeFH cases were detected in Canterbury, with 2-3% of cases detected nationally. Members considered there was a risk that HeFH patients would be misdiagnosed and treated inappropriately as having mixed dyslipidaemia. Members noted it had seen no data on the prevalence of FH in New Zealand, but considered it was likely that New Zealand has similar rates as overseas, although the condition is genetic. Members noted that there is a higher prevalence in Afrikaaner South Africans. The Committee had seen no data on the prevalence in Māori and Pacific people. The Committee noted that HoFH is a rare disease; members considered there may be only three such patients in New Zealand.
- 10.6 The Committee noted that evolocumab is indicated in adults with primary hyperlipidaemia or mixed dyslipidaemia, and so the application related only to a subset of the registered indications.
- 10.7 The Committee noted that the goal of treatment of FH, in international guidelines (such as the UK NICE FH guideline) is to achieve at least a 50% reduction in LDL-C concentration from baseline. The Committee considered that this can be achieved through the use of high doses of potent statins such as atorvastatin, and that ezetimibe can be added to a statin if sufficient LDL-C reduction is not achieved by a statin alone (IMPROVE-IT trial). Members noted health outcome models that supported that reduction in cholesterol leads to reduction in cardiovascular events.
- 10.8 The Committee considered that the appropriate comparator for the patient group described in the application would be a high dose statin, perhaps with both the intervention and comparator taking ezetimibe as well.
- 10.9 The Committee reviewed the evidence provided in the application. The Committee

considered that the most relevant evidence came from the FOURIER trial (Sabatine et al N Engl J Med 376:18 1713-22), as it examined cardiovascular disease (CVD) outcomes rather than surrogate endpoints such as LDL-C lowering at 12 weeks.

10.10 With regards to the FOURIER trial, the Committee noted that FH was not an entry criteria of the trial. Members noted that the median follow up was 26 months, and expressed concern at the relatively short follow up compared with other CVD trials which typically have around 5 years of follow up. The Committee noted that only 5% of patients in the trial were on ezetimibe and considered this may not reflect New Zealand treatment regimens as ezetimibe would likely be used in combination with a high dose potent statin for FH management in New Zealand. The Committee considered that patients in this trial had lower baseline LDL-C levels than in other CVD trials. The Committee noted that the trial only recruited patients who had had a cardiovascular event (secondary prevention), whereas the application proposed funding for primary prevention as well. The Committee also noted that patients intolerant to statins were excluded but the proposed funding restrictions would include such patients.

10.11 The Committee noted that the FOURIER trial reported a statistically significant lower rate of its primary endpoint (major CVD events) (hazard ratio 0.85, 95% CI 0.79-0.92). However, the Committee considered the absolute risk reduction was small (1.5%). Members considered that while the median follow up was only 26 months, the available data indicated that the trend would continue. However, members noted that this endpoint was a combination of five events and considered that because these events had significantly different impacts, ranging from minor angina to death that, in common with other combined end-point outcome variables, meant that the robustness of this primary endpoint was uncertain. The Committee noted that the study did not report an improvement in death from any cause in patients taking evolocumab (hazard ratio 1.04, 95% CI 0.91-1.19). The Committee also noted that hazard of cardiovascular death was not improved (hazard ratio 1.05, 95% CI 0.88-1.25). The Committee considered that overall survival was a more important outcome than a reduction in major CVD events or reduction in CVD deaths. The Committee discussed subgroups of the FOURIER trial and considered that there was only a very small absolute risk reduction (0.2%) in the primary outcome in the subgroup of patients taking a statin and ezetimibe (hazard ratio 0.98, 95% CI 0.74-1.31), but also considered that this group was a small subset of the trial population and so may not be a relevant analysis.

10.12 The Committee considered that overall, there is good quality evidence that evolocumab reduced LDL-C levels, and moderate quality evidence that evolocumab reduces risk of major CVD events albeit with a small absolute risk reduction. However, the Committee considered that evolocumab did not improve overall survival and that evidence was weak in FH and absent in a primary prevention population, which makes up the indication under consideration.

10.13 The Committee noted a Cochrane review of PCSK9 inhibitors including evolocumab. The Committee noted that the Cochrane review excluded all of the supplier's submitted trials except the FOURIER trial as all other trials had too short a follow up period (12 weeks). The Committee noted that the review reported that compared with placebo, PCSK9 inhibitors decreased the risk of CVD events with moderate evidence but probably had little or no effect on mortality, and compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect on CVD risk albeit with considerable uncertainty. The Committee also noted that PCSK9 inhibitors had higher risk of adverse events.

10.14 The Committee noted that evolocumab was an injected medicine, but considered that self-

injection would not be an issue in most patients. The Committee considered that funding evolocumab would be unlikely to decrease use of other medicines as it would be prescribed in conjunction with existing treatments. The Committee considered that, should evolocumab be funded, there would be increased pressure on cascade screening, since the availability of a new drug would increase desire to test for the condition.

10.15 The Committee noted the assessments done by PBAC in Australia, SMC in Scotland, and NICE in the UK. The Committee noted that recommendations varied and often related to non-FH conditions.

10.16 The Committee considered that the application to fund evolocumab for HeFH should be declined, noting the trials' use of a composite CVD outcome measure (major CVD events) as the primary endpoint, the lack of a decreased overall death rate in the FOURIER trial, the high cost, and that the available evidence was only for secondary prevention, not primary prevention.

10.17 The Committee considered that given the very small size of the HoFH population it would more appropriate to allow NPPA) applications for this group to be considered by PHARMAC, unless evolocumab was being listed for another group. Members considered that the need of HoFH patients was higher than for HeFH. The Committee considered that any NPPA applications should be required to provide rigorous evidence that the patient had HoFH.

11 Whole thyroid extract and normal and extended release T3 for the treatment of hypothyroidism

Application

11.1 The Committee reviewed an application from the Thyroid Association of New Zealand Incorporated for the funding of whole thyroid extract, and normal and extended release T3 for the treatment of hypothyroidism.

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

Recommendation

11.3 The Committee **recommended** that whole thyroid extract and other T3 containing treatments for the treatment of hypothyroidism be declined.

Discussion

11.4 The Committee noted that application requested funding of three different products for first line treatment of hypothyroidism: animal derived whole thyroid extract (which contains T1, T2, T3, T4 and calcitonin), synthetic triiodothyronine (LT3, normal and sustained release options), and synthetic T3/T4 combination (LT3/4). Members noted that none of the products are registered by Medsafe for use in New Zealand. The Committee noted that whole thyroid is available as a compounded medicine and can be provided by a number of pharmacies in New Zealand.

11.5 The Committee noted that the applicant indicates that there is a subgroup of approximately 16% of patients with hypothyroidism, according to patient survey data, who require the inclusion of triiodothyronine (T3) in their treatment regime in order to achieve complete symptom relief.

11.6 The Committee noted that the applicant has requested funding of T3 containing treatments for a subgroup of patients with hypothyroidism that meet one of the following categories: 1) poor converters of T4 to T3, 2) have faulty DIO1 and/or DIO2 genes, 3) have Hashimoto's thyroiditis and antibodies have not stabilised 4) post-partum thyroiditis patients who do not respond to T4 only treatments, 5) have had thyroidectomy and do not respond to T4 only treatments and 6) patients who experience adverse reactions of no symptom relief or partial symptom relief when on T4 treatments.

Evidence

11.7 The Committee reviewed the evidence provided in support of the submission including the following publications:

- Grozinsky-Glasberg, et al. J Clin Endocrinol Metab. 2006;91(7):2592
- Escobar-Morreale et al. J Clin Endocrinol Metab. 2005;90(8):4946
- Hoang, et al. J Clin Endocrinol Metab. 2013;98(5):1982-90
- Hennessey, et al. Int J Clin Pract. 2018;72(2). doi: 10.1111/ijcp.13062
- Panicker, et al., J Clin Endocrinol Metab. 2009;94(5):1623
- Appelhof, et al. J Clin Endocrinol Metab. 2005;90(11):6296
- Wouters, et al. Thyroid. 2017;27(2):147

11.8 Members noted that there was only one publication that assessed the efficacy of whole thyroid extract (Hoang et al. 2018).

11.9 The Committee noted that international guidelines, including the American Thyroid Association and European Thyroid Association guidelines, state that levothyroxine (T4) should remain the standard of care for treating hypothyroidism and note that no consistently strong evidence for the superiority of alternative preparations e.g. levothyroxine-liothyronine combination therapy, thyroid extract therapy, or other modes of treatment, had been found over monotherapy with levothyroxine, in improving health outcomes.

11.10 The Committee considered that there was a lack of evidence to suggest that T3 containing treatments would provide benefit for the treatment of hypothyroidism and considered that there was some evidence to suggest that treatment with T3 may provide additional risks.

11.11 The Committee considered that the overall quality of evidence for the use of T3 and whole thyroid extract for the treatment of hypothyroidism was poor to moderate; and that there was considerable uncertainty as to the possible effects reflected in wide large confidence intervals for estimates of effects reported in currently available literature. The Committee considered it was not possible to conclude that treatment with T3 met criteria for non-inferiority compared to standard treatment with levothyroxine (T4).

11.12 Members considered that identified literature was consistent with a difference between the effect of animal-derived whole thyroid as compared to synthetic versions, and in particular studies with masking of participants as to treatment allocation, reported that masked research participants had a preference for non-synthetic products. However, members also noted that the nature of the product is such that there is not standardised production between batches and their formal regulatory classification means that they are not under the oversight of Medsafe regulation. Members considered that the lack of a standardised registered product would likely present difficulties if funding of such a product were to be progressed to

Schedule.

- 11.13 The Committee considered that there was no evidence that funding of T3 containing products for the treatment of hypothyroidism would provide any savings to the healthcare system.
- 11.14 The Committee noted the evidence regarding polymorphisms in type 2 deiodinase and response to thyroid therapy and considered that there was currently insufficient clinical evidence to use polymorphisms to guide therapy. The Committee also considered that this approach was not supported by endocrinologists.
- 11.15 The Committee considered that there was potentially a small group of patients who could benefit from treatment with T3 and, while not the subject of the request by the current applicant, there may be a role for T3 augmentation for major depressive episodes or treatment resistant depression.
- 11.16 The Committee suggested that advice be sought from the Mental Health Subcommittee regarding the efficacy of T3 containing treatments for hypothyroid patients with severe depression who are still symptomatic while on levothyroxine treatment, and for augmentation for non-hyperthyroid patients with severe treatment-resistant depression.