

PTAC meeting held on 4 and 5 May 2017

(minutes for web publishing)

PTAC minutes 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 PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

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.

Table of Contents

1. Subcommittee Minutes	3
2. Matters Arising/Correspondence	4
<i>Somatropin</i>	4
<i>Pembrolizumab</i>	4
<i>Paliperidone</i>	4
<i>Eplerenone</i>	5
<i>Zoster Vaccine</i>	5
3. [Withheld in the interim pending further clinical review]	6
4. D-Mannose – Urinary Tract Infections	6
<i>Application</i>	6
<i>Discussion</i>	6
5. Pembrolizumab – Advanced PD-L1 positive non-small cell lung cancer, first line	8
<i>Application</i>	8
<i>Recommendation</i>	8
<i>Discussion</i>	8
6. Olaparib – BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer	12
<i>Application</i>	12
<i>Recommendation</i>	12
<i>Discussion</i>	12
7. Furosemide – Paediatric congenital heart disease	15
<i>Application</i>	15
<i>Recommendation</i>	16
<i>Discussion</i>	16
8. Anti-VEGF	18
Anti-VEGF for 2nd line wAMD	18
<i>Application</i>	18
<i>Recommendation</i>	18
<i>Discussion</i>	18
Ranibizumab for 2nd line DMO	21
<i>Application</i>	21
<i>Recommendation</i>	21
<i>Discussion</i>	21
9. Tiotropium bromide – severe asthma (resubmission)	24
<i>Application</i>	24
<i>Recommendation</i>	25
<i>Discussion</i>	25
10. Secukinumab – Severe plaque psoriasis	27
<i>Application</i>	27
<i>Recommendations</i>	27
<i>Discussion</i>	28

1. Subcommittee Minutes

Nephrology Subcommittee

- 1.1 The Committee noted that the complete record of the Nephrology Subcommittee of PTAC meeting held on 6 December 2016 was not yet finalised and will be considered at the next PTAC meeting, however two sections of the minutes, item 6 and 7, were provided to the Committee for consideration.
- 1.2 The Committee noted and accepted recommendations related to item 7, regarding widening access to enoxaparin in community dialysis if cost neutral to the Combined Pharmaceutical Budget. The Committee noted PHARMAC are currently consulting on a proposal to widen access to enoxaparin for this indication.
- 1.3 The Committee noted item 6, Matters Arising, regarding the current funding of cinacalcet and the previous recommendations of the Committee. The Committee also noted a letter dated 9 February 2017 (received 13 March 2017) sent to PHARMAC's Medical Director from five Subcommittee members raising concerns about access to cinacalcet for patients with severe symptomatic secondary/tertiary hyperparathyroidism.
- 1.4 The Committee noted the issues raised by Subcommittee and thanked them for their input.
- 1.5 The Committee considered that all available evidence regarding the use of cinacalcet was taken into account in the Committee's previous recommendation to decline funding for use in primary, secondary and tertiary hyperparathyroidism with symptomatic hypercalcaemia including those patients contraindicated to surgery or where previous surgery has been unsuccessful, regardless of whether or not the patient is on dialysis. The Committee noted the recommendation was based on the lack of evidence of a long-term clinical benefit in these patients. The Committee noted that the views of both the Endocrinology and Nephrology Subcommittees were taken into account in making its recommendations regarding funding for cinacalcet.
- 1.6 The Committee noted the use of cinacalcet in patients post renal transplant with severe hypercalcaemia requiring treatment as a bridge to parathyroidectomy has not previously been considered and that a funding application for this indication supported by evidence for its use in this setting would be welcomed.
- 1.7 The Committee noted that the Named Patient Pharmaceutical Assessment pathway is available for individual patients whose clinical circumstances have not been previously considered for a schedule listing.
- 1.8 The Committee noted that the funding of cinacalcet for indications which have already been considered for schedule listing can be re-considered upon provision of new evidence to support its use in these settings.
- 1.9 The Committee noted the Subcommittee's view regarding the current access criteria for cinacalcet for patients with calciphylaxis particularly in regards to the level of hypercalcaemia and previous treatment with sodium thiosulphate and bisphosphonates. The Committee acknowledged the expert opinion of the nephrologists on the Subcommittee that the serum calcium level may not be suitable for determining access to cinacalcet treatment. The Committee supported the proposed changes suggested by the Subcommittee and agreed that the calcium level requirement and prior lines of treatment should be removed. However, the Committee noted that PHARMAC staff would need to determine the potential impact of this change on patient numbers, expected uptake and additional costs.

2. Matters Arising/Correspondence

Somatropin

- 2.1 The Committee noted correspondence from the Prader-Willi Syndrome Association (NZ) Inc. regarding funding of somatropin for adult patients with Prader-Willi Syndrome.
- 2.2 The Committee noted that at its meeting in November 2016 it had recommended that the application to widen access to somatropin to include treatment of adults and adolescents with PWS with skeletal maturity as defined by a bone age >14 years (female patients) or >16 years (male patients) adults be declined due to a lack of evidence for clinically meaningful long-term benefit.
- 2.3 The Committee noted that somatropin was currently funded for children with Prader-Willi Syndrome from 6 months of age and a bone age <14 years (female patients) or <16 years (male patients).
- 2.4 The Committee considered that all available evidence regarding the use of somatropin in adult patients with Prader-Willi Syndrome was taken in to account in the Committee's previous recommendation to decline funding for this patient group.
- 2.5 The Committee considered that although there appeared to be some benefit from treatment with somatropin, this was from relatively short term studies and of a magnitude that would not translate into clinically meaningful benefit.
- 2.6 The Committee would welcome new published evidence to support the use of somatropin in adult patients with Prader-Willi Syndrome.

Pembrolizumab

- 2.7 The Committee noted correspondence from Merck Sharpe and Dohme (NZ) Limited regarding the November 2016 PTAC minute for pembrolizumab for patients with previously treated non-small cell lung cancer (NSCLC).
- 2.8 The Committee considered that there remained uncertainty regarding the use of PD-L1 expression to target treatment and the comparability of results obtained with different diagnostic platforms.
- 2.9 The Committee noted unpublished data of longer-term follow-up from KEYNOTE010 (Herbst et al. World Conference Lung Cancer, December 2016). The Committee noted that there were very few subjects beyond two years, the majority of subjects who completed 2 years of treatment had initially had a complete or partial response, and 4% of subjects had disease progression after stopping pembrolizumab treatment. The Committee considered that, from the data provided, a survival plateau did not appear to have been reached.
- 2.10 The Committee noted that the funding application for the use of pembrolizumab for previously untreated PD-L1 positive NSCLC patients was on the agenda for consideration at this meeting.

Paliperidone

- 2.11 The Committee noted correspondence from Janssen-Cilag Pty Ltd regarding the Mental Health Subcommittee minute of November 2016 regarding paliperidone 3-monthly depot injection.
- 2.12 The Committee acknowledged that while the between-patient difference in metabolic rates may affect pharmacokinetic data, it considered this would not have a significant therapeutic impact. The Committee reiterated that risperidone and paliperidone are considered essentially the same chemical, with the same mechanism of action, safety

profile and efficacy outcomes.

Eplerenone

- 2.13 The Committee considered the resubmission and correspondence from the applicant regarding eplerenone. The Committee noted that as part of the resubmission the applicant proposed that eplerenone be funded for patients with heart failure with an ejection fraction (EF) of less than 40% and serum potassium of less than 4.0 mmol/L or greater than 5.5 mmol/L.
- 2.14 The Committee considered the evidence in the submission including Vardeny et al (*Circ heart Fail.* 2014; 7:573-9) and Roush et al (*J Hypertens.* 2015;34:11-9). The Committee considered the strength of the evidence provided was low as both studies were post-hoc analyses. The Committee considered that there was no direct evidence to support an additional health benefit for eplerenone compared with spironolactone for the group proposed in the resubmission. The Committee reiterated its previous advice that it would like to review the results of the SNOW trial when these become available, and considered that the results of this trial may be relevant to considering the group proposed in the resubmission. The Committee considered that although the population included in the SNOW trial was heart failure patients with glucose intolerance or type 2 diabetes, that it would be of interest, as it would be the first trial to date which is a direct comparison between the two treatments.
- 2.15 The Committee noted its previous recommendation, from August 2016, that eplerenone should be funded with a low priority for patients with heart failure with an ejection fraction of less than 40% who are intolerant to optimal dosing of spironolactone. The Committee considered that its previous recommendation stands. The Committee clarified that 'intolerant' would include any patients who have experienced clinically significant adverse effect from optimal dosing of spironolactone. The Committee considered that a significant adverse effect could be defined as painful gynaecomastia, significant hyperkalaemia, or clinically relevant renal impairment.
- 2.16 The Committee noted that PHARMAC sought advice on the size of the population that could be classed as intolerant to optimal dosing of spironolactone. Members considered that 5-10% of patients taking spironolactone may experience painful gynaecomastia, significant hyperkalaemia, clinically relevant renal impairment or other adverse effects despite optimal dosing. Members considered that information from the RALES trial (Pitt et al. *NEJM* 1999;341:709-17) and the more recent randomised controlled trials for valsartan/sacubitril, considered at its February 2016 meeting, may provide a more certain estimate for number of patients that experience adverse effects from spironolactone such as hyperkalaemia and renal impairment.

Zoster Vaccine

- 2.17 The Committee considered the results of a recent retrospective cohort study (Izurieta et al *CID* 2017;64(6):785-93) of the MSD zoster vaccine (Zostavax), which had been published after PTAC's most recent considerations (February 2016) regarding the funding application and cost-utility analysis for zoster vaccine. Members noted that the study analysed administrative reimbursement data to examine vaccine effectiveness and duration of protection provided by zoster vaccination in nearly a million individuals aged 65 and over in the United States. Members noted measured outcomes included outpatient herpes zoster, hospitalised herpes zoster, outpatient ophthalmic zoster, and postherpetic neuralgia (PHN).
- 2.18 The Committee considered that in addition to the inherent limitations of retrospective cohort studies. In particular this study may not be representative of the New Zealand patients because the study considered individuals that made insurance claims and the mean age of individuals was 77 years which is appreciably older than likely mean ages of patients proposed for any funding in New Zealand. The Committee also noted that follow-up times

were inconsistent or incomplete, including 17% who were lost to follow-up on entering institutional care. Members noted that the Committee had previously commented that efficacy of vaccination wanes in older age groups. The Committee considered the new study was difficult to apply to the New Zealand population and proposed funding setting, and felt that the evidence provided by prospective randomised controlled vaccine efficacy trial, considered in February 2016, provided a more robust assessment of vaccine efficacy.

- 2.19 The Committee noted vaccine efficacy in the cohort study was of a similar magnitude to that modelled by PHARMAC based on Oxman et al. (N Engl J Med 2005;352:22), with overlap between the two sets of confidence intervals. The Committee considered that the new evidence did not change its previous recommendations that zoster vaccine be listed on the Pharmaceutical Schedule for vaccination of people aged 65 with a medium priority and with a 2-year catch-up programme for people aged between 65 and 80 years with a low priority.
- 2.20 The Committee noted that another zoster vaccine supplied by GSK was in the pipeline and the results of the randomised trial of this vaccine should be considered by PTAC when available.

3. [Withheld in the interim pending further clinical review]

4. D-Mannose – Urinary Tract Infections

Application

- 4.1 The Committee considered the application from Te Arai Biofarma for D-mannose (Urofem) for prevention and treatment of acute uncomplicated cystitis during pregnancy or associated with neurogenic bladder
- 4.2 The Committee **recommended** that the application from Te Arai Biofarma for the funding of Urofem for prevention and treatment of acute uncomplicated cystitis during pregnancy or associated with neurogenic bladder be **declined**.
- 4.3 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 4.4 The Committee noted that the proposed mechanism of action of D-mannose is the binding of the sugar to the lectin receptor of urothelium cells to prevent the adhesion of pathogenic bacteria.
- 4.5 The Committee noted that the standard of care to treat uncomplicated cystitis in New Zealand is trimethoprim 300 mg/day for 3 days if the patient presents with symptoms of uncomplicated cystitis and has a positive midstream specimen or urine dipstick. Alternatives are nitrofurantoin 50 mg four times per day for 7 days or cephalexin 250 mg twice daily for 7 days.
- 4.6 For pregnant women, Members noted that trimethoprim 300 mg/day for 7 days can be used in the 2nd or 3rd trimesters, otherwise nitrofurantoin 50 mg four times per day for 7 days (<36 weeks) or cephalexin 250 mg twice daily can be used. Members considered that the treatment of cystitis in patients with neurogenic bladder to be complex, since colonisation of the urothelium frequently occurs in patients who catheterise; the decision to prescribe is usually made by having objective clinical evidence as well as microbiological evidence of infection; antibiotic choice is guided by sensitivities from MSU culture; and that ciprofloxacin 500 mg twice daily for 7 days is also an option for this cohort of patients. Members noted that nitrofurantoin 50 mg daily is sometimes used for prophylaxis, and considered there should be no problem with access or availability of these antibiotics for treatment of urinary tract infections (UTIs) in New Zealand.

- 4.7 The Committee noted that the evidence provided in the submission was of weak strength and poor quality, which provided little support for the use of D-mannose for the indications requested by the applicant. Members noted that D-mannose was evaluated in one randomised clinical trial and two single-centre pilot studies. There were no RCTs in pregnancy. There were no RCTs in patients with neurogenic bladder.
- 4.8 Members reviewed the results of a randomised trial for D-mannose prophylaxis for recurrent UTIs in women (Kranjcec B et al. *World J Urol.* 2014;32:79-84); the study randomised 308 women to receive prophylaxis with 2 g of D-mannose powder in water daily (n=103), 50 mg nitrofurantoin daily or did not receive anything for six months. Members noted that the trial had an unusual study design for a prophylaxis trial; the number of recurrences per patient/year were unable to be calculated because patients were excluded from the study following first occurrence of a UTI. Overall, 98 patients had recurrent UTIs, with 15 (14.6%) in the D-mannose group, 21 (20.4%) in the nitrofurantoin group and 62 (60.8%) in the group that did not receive prophylaxis. D-mannose and nitrofurantoin significantly reduced the risk of recurrent UTIs, but there was no difference between D-mannose and nitrofurantoin (RR 0.714, 95% CI 0.391–1.306). Members raised a number of concerns regarding the study. Specifically, UTIs were not diagnosed microbiologically by pyuria, which is performed to differentiate the microorganisms causative of UTIs from contaminants, and accordingly, *Enterococcus* was listed as a causative organism in some patients, while it is frequently a contaminant. Further, study participants were not blinded and there was no placebo control. While results were encouraging, the Committee agreed with the study authors who commented that more studies will be needed to validate the results.
- 4.9 The Committee reviewed the results of a pilot study that assessed the efficacy of D-mannose for the prevention and treatment of recurrent UTIs (Porru D et al. *J Clin Urol.* 2014;7:208-13); 60 female patients were randomly assigned to oral 1 g of D-mannose three times a day for 2 weeks and then 1 g twice a day for 22 weeks or antibiotic treatment with trimethoprim/sulfamethoxazole 160/800 mg twice a day for 5 days and then a single dose daily for 1 week per month for 23 weeks. At 24 weeks, patient groups crossed over and switched groups. Members noted treatment with D-mannose had a significantly increased time to recurrence (200 days) compared with antibiotic treatment (52.7 days), but considered that the study had an unusual design and a number of issues that made it difficult to interpret the data. Members noted that time to resolution of symptoms was not reported, only patients in the D-mannose group were required to alkalinise their urine, which created an important confounder, and compliance and safety were not reported. Members considered that this study using co-trimoxazole as the comparator was not transferrable to the New Zealand clinical setting.
- 4.10 The Committee also reviewed the results of an observational pilot study (Domenici L et al. 2016;20:2920-5). Forty-three women with symptomatic acute cystitis were treated with 1.5 g D-mannose twice daily for 3 days and then once a day for 10 days. The Committee noted that the primary endpoint was improvements in a questionnaire that assessed the severity of UTI symptoms. Members noted that the study was not blinded, there was no control nor placebo group included. and treatment with D-mannose also required the patients to alkalinise their urine.
- 4.11 The Committee considered that D-mannose is a biologically-plausible alternative to antibiotics to treat and prevent recurrent cystitis, particularly with the increasing concern regarding antibiotic resistance. Members noted that D-mannose appears well tolerated and there is an unmet clinical need for effective and safe non-antibiotic alternatives to treat UTIs.
- 4.12 Members estimated that the number of patients on prophylactic antibiotics would be small and suggested that were this medication to be recommended for funding, PHARMAC should investigate the number of patients taking once daily nitrofurantoin for prophylaxis.

4.13 The Committee noted that the lack of pharmacokinetic data is concerning and Urofem is not registered through Medsafe. The Committee noted that there was no data for efficacy or safety for the use of D-mannose in pregnancy or neurogenic bladder. The Committee would welcome reviewing new, good quality evidence, for D-mannose when it becomes available.

5. Pembrolizumab – Advanced PD-L1 positive non-small cell lung cancer, first line

Application

5.1 The Committee considered an application from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab (Keytruda) as monotherapy for patients with metastatic, unresectable, stage III and IV (advanced) non-small cell lung cancer (NSCLC) whose tumours express programmed death ligand 1 (PD-L1) at a level of $\geq 50\%$ in a first-line setting for EGFR wildtype patients and second-line for EGFR positive patients.

Recommendation

5.2 The Committee **deferred** making a recommendation regarding the funding of pembrolizumab as a first-line treatment for patients with PD-L1 positive NSCLC pending publication of mature survival data and further information regarding the use of PD-L1 expression as a biomarker.

Discussion

5.3 The Committee noted that at its meeting in May 2016 PTAC had considered the funding of another PD-1 inhibitor, nivolumab (Opdivo, Bristol Myers-Squibb), for the treatment of locally advanced or metastatic NSCLC in the second and third line settings and had recommended funding with low priority.

5.4 The Committee noted that at its meeting in November 2016, PTAC had considered the funding of pembrolizumab as monotherapy for the second or third-line treatment of locally advanced, or metastatic, unresectable NSCLC whose tumours express PD-L1 at a level of $\geq 1\%$. The Committee noted that it had recommended pembrolizumab be funded in this setting with low priority due to: the significant immaturity of currently available data, uncertainty that the observed trial-based improvements translate to long-term clinically meaningful overall survival gains, and significant uncertainty regarding the optimal duration of treatment.

5.5 The Committee noted that at its meeting in March 2017 CaTSoP had considered the applications for pembrolizumab for previously untreated (first line) and previously treated (second and third line) advanced NSCLC. The Committee noted that CaTSoP had recommended pembrolizumab be funded for:

- the first-line treatment of patients with previously untreated advanced NSCLC whose tumours express PD-L1 at a level of $\geq 50\%$ with a low priority, subject to Special Authority criteria being met.
- the second or third-line treatment of patients with previously treated advanced NSCLC whose tumours express PD-L1 at a level of $\geq 1\%$ with a low priority, subject to Special Authority criteria being met.

5.6 The Committee noted that pembrolizumab and nivolumab are both currently funded for the treatment of patients with locally advanced or metastatic melanoma.

5.7 The Committee noted that lung cancer is the fifth most common cancer registration in 2013 with NSCLC comprising up to 70% of these in New Zealand. The Committee noted that the majority of NSCLC patients present with advanced stage III or IV disease at diagnosis.

- 5.8 The Committee noted that survival rates for patients with advanced NSCLC are poor with currently funded treatments; the 1-year survival for patients with stage IV disease treated with chemotherapy is 10%.
- 5.9 The Committee noted that lung cancer registration and mortality rates are consistently higher for Māori when compared with non-Māori.
- 5.10 The Committee noted that pembrolizumab is registered in New Zealand as monotherapy for NSCLC patients:
- as first-line treatment for metastatic NSCLC patients whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations; and
 - as second-line treatment or beyond for advanced NSCLC patients with a TPS of $\geq 1\%$ who have received prior platinum-containing chemotherapy and, if applicable, targeted treatment for EGFR or ALK mutation.
- 5.11 The Committee noted that the registered dose for previously untreated NSCLC is a 200 mg flat dose which differs from the 2 mg/kg registered dose for melanoma or previously treated NSCLC patients. Members considered that the Committee had not seen any primary data to support the rationale for the flat dose as opposed to weight based dosing, and the clinical reason for the change was unclear. Members considered that a 200 mg flat dose would result in an increase in the milligrams per dose for the average population; and a significant increase for NSCLC patients who typically have a low average body weight.

Evidence

- 5.12 The Committee noted evidence from KEYNOTE-024; the pivotal trial for the use of pembrolizumab in previously untreated NSCLC. The Committee noted that KEYNOTE-024 is a randomised, open-label, phase 3 study of 35 cycles of pembrolizumab (fixed dose 200 mg every 3 weeks, n=154) compared to 4-6 cycles of investigators choice of platinum chemotherapy (carboplatin or cisplatin plus pemetrexed, carboplatin or cisplatin plus gemcitabine, or carboplatin plus paclitaxel, n=151) in patients with previously untreated stage IV NSCLC with high PD-L1 positive (PD-L1 expression $\geq 50\%$) without EGFR mutation or ALK translocation (Reck et al. NEJM 2016;375:1823-33).
- 5.13 The Committee noted that eligibility criteria included no prior systemic therapy for metastatic disease, ECOG 0-1, a life expectancy of at least 3 months, at least one measurable lesion according to RECIST. The Committee considered that on average the New Zealand NSCLC population would likely have a higher ECOG status (worse health) than the study population.
- 5.14 The Committee noted that exclusion criteria included active interstitial lung disease, or a history of pneumonitis for which they had received glucocorticoids, current treatment with systemic glucocorticoids, and untreated brain metastases.
- 5.15 The Committee noted that 18.4% of the original screened study population went onto trial and that around 200 screened patients with PD-L1 TPS $\geq 50\%$ did not proceed onto study treatment. The Committee noted that based on available published trial data the reason for this was unclear but considered it was likely because these patients had clinically deteriorated in the time between screening and start of the study such that they were unable to progress on trial. The Committee considered in clinical practice there would be a much shorter duration between screening and starting treatment and therefore this level of drop-out would likely be less.

- 5.16 The Committee noted that study patients with disease progression as per RECIST in the chemotherapy arm could cross over to receive pembrolizumab, and that while crossover was not permitted from the pembrolizumab arm there were no guidelines regarding therapy after disease progression for these patients. The Committee noted that at the time of data cut-off 43.7% of the patients in the chemotherapy arm had crossed over to receive pembrolizumab after disease progression and of these patients 57.6% were still receiving pembrolizumab.
- 5.17 The Committee noted that patients in either treatment group who were in clinically stable condition and were considered by the investigator to be deriving clinical benefit could continue therapy after disease progression.
- 5.18 The Committee noted that on the basis of the second interim analysis (data cut-off 9 May 2016) with less than 12 months of follow-up the safety monitoring committee recommended that the trial be stopped and patients remaining in the chemotherapy arm be offered pembrolizumab.
- 5.19 The Committee noted that median duration of treatment was 7.0 months or 10.5 cycles in pembrolizumab arm (range 1 day to 18.7 months) and 3.5 months or 4 cycles in the chemotherapy arm (1 day to 16.8 months). The Committee noted that at the time of data cut-off, 48% of pembrolizumab patients and 10% of chemotherapy patients were still receiving study treatment.
- 5.20 The Committee noted that at a median follow-up of 11.2 months, median progression-free survival (PFS), the primary end-point, was 10.3 months (95% CI, 6.7-NR) in the pembrolizumab arm and 6.0 months (95% CI, 4.2-6.2) in the chemotherapy arm (HR for disease progression or death, 0.50; 95% CI, 0.37-0.68; $p < 0.0001$). The Committee noted that at 12 months there were only 22 and 9 patients still in the pembrolizumab and chemotherapy arms respectively.
- 5.21 The Committee noted that estimated PFS at 6 months was 62.1% (53.8-69.4) in the pembrolizumab arm and 50.3% (41.9-58.2) in the chemotherapy arm. The Committee noted that the estimated OS at 6 months was 80.2% (72.9-85.7) in the pembrolizumab arm and 72.4% (64.5-78.9) in the chemotherapy arm. The Committee noted the median overall survival was not reached in either group. The Committee considered the survival benefit for pembrolizumab treatment was highly uncertain.
- 5.22 The Committee noted that the most common grade 3, 4, or 5 treatment-related adverse events were diarrhoea (3.9%), pneumonitis (2.6%) in the pembrolizumab arm and anaemia (19.3%), neutropenia (13.3%) in the chemotherapy arm. The Committee noted that immune-mediated adverse events occurred in 29.2% of patients in the pembrolizumab arm and 4.7% in the chemotherapy arm with events of grade 3 or 4 occurring in 9.7% and 0.7% respectively.
- 5.23 The Committee considered that due to the relatively short duration of follow-up this likely under-represented the adverse immune effects of treatment with pembrolizumab which could be significant and persist life-long. Members considered that longer-term follow up would likely show an increase in autoimmune toxicity. Members considered there is a growing signal in the melanoma population that a longer duration of immune checkpoint inhibitor treatment is correlated with an increased likelihood of developing immune-mediated side effects. Members considered that significant health sector resource may be required to manage patients with immune-mediated side effects.
- 5.24 Overall, the Committee considered that due to the very immature nature of the data presented to support pembrolizumab for patients with previously untreated NSCLC there was a high level of uncertainty regarding the benefit and risks of pembrolizumab for previously untreated NSCLC patients.

PDL1 expression

- 5.25 The Committee noted that the proposed population would require patients to undergo PD-L1 expression testing to determine eligibility for treatment.
- 5.26 The Committee noted that that while PD-L1 testing is not currently routinely carried out in New Zealand laboratories, the supplier indicates they are undertaking a programme to establish immunohistochemistry (IHC) PD-L1 testing facility in New Zealand. The Committee noted that the suppliers program included validation provided by the Peter MacCallum Cancer Centre in Melbourne, however, whether there was a plan for ongoing cross validation was unclear.
- 5.27 The Committee noted that based on information regarding the suppliers program it appeared PD-L1 tests and platforms in New Zealand would be lab-developed rather than using a Dako-based diagnostic staining platform, as per the KEYNOTE trials. The Committee considered that the use of lab-developed testing platforms could potentially have a strong impact the outcome of PD-L1 testing. The Committee noted that the current plan could result in different centres implementing different testing platforms and protocols. The Committee noted that without a standardised and regulated PD-L1 testing mechanism and platform it could increase health inequities for NSCLC patients in New Zealand.
- 5.28 The Committee noted that there were ongoing studies aimed at providing information on the analytical and clinical comparability of different PD-L1 IHC assays used in clinical trials. Members noted from information provided by the applicant that both the Blueprint and RING Assay Comparison Projects were comparing PD-L1 test results from various platforms in NSCLC tumours.
- 5.29 The Committee considered that based on current literature it appears there is significant variability in PD-L1 expression between tumour cell types, the cell of origin, and at different times during the disease course. The Committee considered that, if eligibility for treatment were determined by a PD-L1 expression threshold, this variability of PD-L1 expression would likely provide clinicians and patients justification to undergo repeat biopsy and PD-L1 expression testing to achieve the desired positive result. The Committee considered repeat testing would add to the health sector costs of pembrolizumab. Members considered that based on the number of patients with TPS<50% it could be expected that up to 50% of NSCLC patients would have multiple biopsies, PD-L1 expression tests, and associated scans.
- 5.30 The Committee noted that the use of PD-L1 as a candidate biomarker for pembrolizumab appears to be based on retrospective analysis of KEYNOTE-001 data of response rates at various TPS levels. The Committee considered that the overall response by PD-L1 expression quartile from KEYNOTE-001 shows that the difference in response did not become significant until a TPS of 50% or greater. The Committee considered that the response rate for patients with TPS <1% was similar in patients with TPS 1%-24% (10.3% and 12.6% respectively).
- 5.31 The Committee considered there was significant uncertainty regarding the use of PD-L1 expression to target treatment and that, given the technical difficulties and associated costs, further information was needed to inform different specific therapy-related PD-L1 cut-offs and the use of alternative staining assays to those validated in the clinical trials.
- 5.32 The Committee noted that the KEYNOTE-042 trial investigating the use of pembrolizumab in treatment naïve NSCLC with PD-L1 expression of 1% or greater was ongoing.

- 5.33 The Committee noted that there were a number of other immune checkpoint inhibitors in late-stage development for the treatment of patients with NSCLC and other tumour types, either as monotherapy or in combination with other treatments.
- 5.34 The Committee considered that, based on evidence for the use of PD1 inhibitors in melanoma and second-line NSCLC previously considered by PTAC, there was likely a class effect from treatment with different immune checkpoint inhibitors; and considered it likely different immune checkpoint inhibitors would have the same or similar effect in the treatment of NSCLC.

6. **Olaparib – BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer**

Application

- 6.1 The Committee considered an application from Astra Zeneca for the funding of olaparib (Lynparza) 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.

Recommendation

- 6.2 The Committee **deferred** making a recommendation regarding the application for the funding of olaparib pending publication of the SOLO-2 study which appears to include further quality of life data.
- 6.3 The Committee **recommended** the application be referred to the Cancer Treatments Subcommittee particularly for advice regarding the availability and practicalities of somatic vs germline BRCA-testing and appropriate Special Authority criteria.

Discussion

- 6.4 The Committee noted that in 2013 ovarian cancer was recorded as the sixth most commonly registered cancer in females and the fifth most commonly registered cancer death for females (178) in New Zealand. The Committee noted that reported survival rates for ovarian cancer in New Zealand at 1, 5, and 10 years are 65%, 36% and 31% respectively.
- 6.5 The Committee noted that majority of ovarian malignancies are derived from epithelial cells and that 75% are of serous histology. The Committee noted that fallopian tube and peritoneal serous carcinoma are considered to be closely related to ovarian carcinomas based upon similarities in histology and clinical behaviour.
- 6.6 The Committee noted that women with BRCA gene mutations have an increased risk of ovarian and breast cancer. The Committee noted that women with BRCA1 and BRCA2, have an estimated lifetime risk of ovarian cancer (at age 70 years) of between 35% and 46% and 13% and 23% respectively compared with a general population risk estimated to be less than 1%.
- 6.7 The Committee noted that symptoms associated with ovarian cancer are non-specific, with the type or severity of symptom not reliably corresponding to disease stage. The Committee noted that approximately 70% of patients are diagnosed with advanced stage III or IV disease and that ovarian cancers in BRCA mutation carriers are more likely to be of higher grade than ovarian cancers in age-matched controls.
- 6.8 The Committee noted that current first-line treatment for ovarian cancer is surgery, with or without radiotherapy, followed by chemotherapy with a platinum agent (carboplatin or cisplatin), either alone or in combination with paclitaxel. However, almost all patients relapse (70% after 2 years); therefore, second-line treatment is usually required, the goal of which is essentially palliative.

- 6.9 The Committee noted that olaparib is an orally administered inhibitor of human Poly-(ADP-ribose) polymerase enzymes, also known as PARP enzymes, which are required for effective repair of DNA.
- 6.10 The Committee noted that olaparib (Lynparza) is indicated as monotherapy for the maintenance treatment of patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy.
- 6.11 The Committee noted that the recommended dose of olaparib is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg until progression of the underlying disease. The Committee noted that the Medsafe datasheet states that olaparib can be administered in patients with mild renal impairment and that the efficacy of hormonal contraception may be reduced by co-administration with olaparib.

Evidence

- 6.12 The Committee noted the key clinical evidence comes from a randomised, double-blind, placebo-controlled phase II trial (Study 19) to evaluate maintenance therapy with olaparib (400 mg twice daily, n=136) or matching placebo (n=129) in 265 patients with platinum-sensitive high-grade (grade 2 or 3) serous, or a serous component, recurrent ovarian cancer (including fallopian tube and peritoneal cancer) (Ledermann et al. NEJM 2012;366:1382-92).
- 6.13 The Committee noted that eligibility criteria included having complete at least two courses of platinum-based chemotherapy, the most recent regimen had induced an objective response as defined by RECIST guidelines version 1.0 or a cancer antigen 125 (CA125) response according to Gynecological Cancer InterGroup criteria.
- 6.4 The Committee noted that at data entry cut-off (June 30, 2010 after 153 progression events in 57.7 of patients) 68 patients (50%) in the olaparib arm and 21 patients (16%) in the placebo arm were still receiving study treatment. The Committee noted that median progression free survival (PFS), the primary endpoint, was 8.4 months in the olaparib arm and 4.8 months in the placebo arm (HR for progression or death, 0.35; 95%CI 0.25-0.49;p<0.001).
- 6.15 The Committee noted that a pre-planned retrospective analysis of data by BRCA mutation status established that the study population included 136 patients who had a known or suspected BRCA mutation (BRCAm) (olaparib, n=74; placebo n=62). The Committee noted that median PFS for BRCAm subgroups was 11.2 months in the olaparib arm and 4.3 months in the placebo arm (HR for progression, 0.18, 95% CI 0.10-0.31; p<0.001) compared to median PFS for BRCA wildtype of 7.4 months in the olaparib arm and 5.5 months in the placebo arm.
- 6.16 The Committee noted that at the interim analysis of overall survival (OS) (data-cutoff point, October 31, 2011) there was no statistically significant difference between the groups regardless of BRCA status or treatment (HR for death in the olaparib arm, 0.94; 95% CI, 0.63 to 1.39; P = 0.75). The Committee noted that median OS (38% data maturity) was 29.7 months in the olaparib arm and 29.9 months in the placebo arm.
- 6.17 The Committee noted that Lederman et al 2012 reported there was no statistically significant between-group differences in disease-related symptoms or rates of improvement in health-related quality of life, based on patient-reported outcomes.
- 6.18 However, the Committee noted that the majority of patients in the placebo arm did not contribute HRQoL data beyond 6 months due to disease progression. The Committee

- noted that based on currently available evidence there was a lack of data to support any quality of life improvements from treatment with olaparib.
- 6.19 The Committee noted an updated analysis of Study-19 reports overall survival (OS) data, a secondary endpoint, from the third data analysis (77% data maturity) after more than 5 years' follow-up of the intention to treat population (Ledermann et al. *Lancet Oncol* 2014;15:852-61).
 - 6.20 The Committee noted that at a median follow-up of 71.0 months (IQR 67.8-72.9) the median OS was 29.8 months [95% CI 26.9–35.7] for those treated with olaparib vs 27.8 months [24.9–33.7] for those treated with placebo), and in patients with BRCAm (HR 0.62 [95% CI 0.41–0.94] nominal p=0.025; 34.9 months [95% CI 29.2–54.6] vs 30.2 months [23.1–40.7]). The Committee noted that OS data in patients with BRCA wild-type were HR 0.83 (95% CI 0.55–1.24, nominal p=0.37; 24.5 months [19.8–35.0] for those treated with olaparib vs 26.6 months [23.1–32.5] for those treated with placebo).
 - 6.21 The Subcommittee noted that dose reduction or dose interruption was more common in the olaparib arm with adverse events more commonly reported in the olaparib arm than in the placebo arm (by more than 10% of patients) were nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), and anaemia (17% vs. 5%).
 - 6.22 The Committee noted that while crossover in this study was not allowed, 17 patients from the placebo group, including 14 with BRCAm, had received post-study PARP inhibitor treatment via other clinical studies by the 2015 data entry cut-off.
 - 6.23 The Committee noted a post-hoc analysis of OS results from interim data (52% maturity in the BRCAm population) from Study 19 adjusted for post-progression use of PARP inhibitors by excluding all patients from the sites where at least 1 patient received post-progression treatment with a PARP inhibitor (Matulonis et al. *Cancer* 2016;122:1844-52). The Committee noted that the resulting patient population consisted of 97 BRCAm patients from 50 sites; 57 in the olaparib arm and 40 in the placebo arm. The Committee noted that the adjusted OS analysis for the BRCAm subgroup resulted in a HR of 0.52 (95% CI, 0.28-0.97; p=0.039) compared to placebo.
 - 6.24 The Committee considered that median OS for olaparib-treated populations were similar whether sites at which post-trial PARP inhibitor treatment was received were excluded or not (median in both cases, 34.9 months). However, median OS outcomes for placebo-treated patients were 26.6 months at sites without post-trial PARP inhibitor access and 31.9 months when sites with a post-trial PARP inhibitor were included. Members acknowledge that while the data was likely to have been confounded by crossover, the value of this analysis was unclear. Members considered that it remained unclear what magnitude of survival benefit (if any) was obtained from olaparib treatment.
 - 6.25 The Committee considered that the evidence for any survival benefit from olaparib as maintenance treatment for patients with relapsed ovarian cancer was of low quality, being from phase 2 trials and retrospective analyses. The Committee considered that based on the currently available evidence any benefit for patients from treatment with olaparib was highly uncertain.
 - 6.26 The Committee acknowledged the increase in time to first subsequent treatment (TFST) and time to second subsequent treatment (TSST) in patients receiving olaparib but considered it remained unclear whether use of olaparib would reduce the total number of platinum-based infusions ovarian cancer patients received.
 - 6.27 The Committee considered that use of olaparib beyond progression at the physician's discretion for participants in Study 19 complicated estimation of duration of treatment for the proposed indication. The Committee considered that TFST could be considered as a proxy for progression and therefore duration of treatment.

- 6.28 The Committee acknowledged the increase in PFS and TFST for women receiving olaparib treatment but in the absence of comparative QoL data over this time the Committee considered it was difficult to quantify the potential benefit for patients of this increase, in the absence of a proven increase in OS.
- 6.29 The Committee noted that the SOLO-2 study, a phase 3 trial assessing maintenance treatment with olaparib tablet formulation in patients with BRCAm and platinum-sensitive recurrent serous ovarian cancer, who have received at least two previous lines of platinum-based chemotherapy, is ongoing and would likely be published later in the year. Members considered that it appeared SOLO-2 would provide additional quality of life data. Members noted that it appeared the dose regimen with the tablet formulation would have a lower pill burden than the current capsule formulation.
- 6.30 The Committee considered that while BRCA testing was available in New Zealand, it was restricted to germline testing only at a cost of around \$450 and there was a relatively limited uptake nationally. The Committee noted that around 15% of patients in Study 19 had somatic BRCAm only and considered that if somatic testing were to be undertaken it would likely be significantly more expensive than germline testing.
- 6.31 The Subcommittee noted that in addition to BRCA1 and BRCA2 there are many other genes involved in DNA repair and a proportion of sporadic ovarian and other cancers, such as breast, share BRCA-like functional abnormalities with those in BRCAm carriers. Members noted that such tumours are referred to as exhibiting 'BRCA-ness'. Members considered that given the activity of PARP inhibitors their use may not be limited to patients with BRCAm and could also extend to a larger number of patients with 'BRCA-ness' who may also seek treatment with BRCA targeted agents such as olaparib.
- 6.32 The Committee noted that international recommendations regarding olaparib as maintenance treatment for ovarian cancer appear to all differ slightly in their definition of the eligible patient group:
- 6.33 The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia had recommended for patients with relapsed, high grade serous, platinum sensitive ovarian cancer and germline BRCAm following 2 or more platinum based regimens;
- 6.34 The National Institute for Health Care Excellence (NICE) in the UK recommendation specified adult patients who have BRCA1 or BRCA2 mutations and have had 3 or more courses of platinum based chemotherapy; and
- 6.35 The Scottish Medicines Consortium (SMC) recommendations was for adult patients with BRCA-mutated (germline and/or somatic) high grade serous ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy.
- 6.36 The Committee noted a letter from the New Zealand Gynaecological Cancer Group in support of the funding of PARP inhibitors for the treatment of ovarian cancer. Members noted that the NZGCG considered there appears to be a class effect from these treatments, particularly for a small group of patients with BRCA-related ovarian cancer, and that there are a number of other PARP inhibitors in late stage development for the maintenance treatment of ovarian cancer.

7. Furosemide – Paediatric congenital heart disease

Application

- 7.1 The Committee considered an application from a clinician for the funding of furosemide 20 mg tablets for paediatric patients with congenital heart disease.

Recommendation

- 7.2 The Committee **recommended** furosemide 20 mg tablets be funded with a **high priority** for paediatric patients with congenital heart disease requiring dosing in 5 mg increments.
- 7.3 The Committee **recommended** PHARMAC provide the details of the minutes to the Medicines Adverse Reactions Committee (MARC) for its information.
- 7.4 The Committee took into account, where applicable, PHARMAC's relevant decision making framework for these recommendations.

Discussion

- 7.5 The Committee noted the request for funding a furosemide 20 mg tablet was based on safety concerns for paediatric patients with regards to the ethanol content of the available liquid preparation. The Committee noted that furosemide 20 mg tablets are not registered with Medsafe.
- 7.6 The Committee noted that the prevalence of congenital heart disease (CHD) ranges from 6-13 per 1000 live births. The Committee noted that furosemide is used in both the acute and chronic treatment of paediatric CHD, before and after corrective surgery, and as a first line treatment for congestive cardiac failure. The Committee noted that the dose may be started at 0.5mg to 1mg/kg three times daily, and increased to 2mg/kg three times daily. The Committee noted that second or third line agents, such as metolazone and/or hydrochlorothiazide, are added as required.
- 7.7 The Committee considered that children with CHD may have other comorbidities including slow weight gain, neurodevelopmental issues, behavioural and emotional problems, and complications from cardiac surgery.
- 7.8 The Committee noted that furosemide is a loop diuretic prescribed for both adults and children. The Committee noted that furosemide oral liquid 10 mg per ml, 30 ml (Lasix) is registered with Medsafe for the treatment of oedema in infants and children. The Committee noted that in 2015 the manufacturer of Lasix (Sanofi) changed the formulation of Lasix from 0.04% ethanol to 10% w/v ethanol (equivalent 100 mg/ml) to improve stability of the product. The Committee noted that the new product can be stored at room temperature and has a longer shelf life.
- 7.9 The Committee noted that Medsafe had approved the change in formulation of the oral liquid for use in infants (which includes the use in neonates), and that Medsafe considered, with regards to the increase in ethanol concentration, that the benefit to risk ratio had not changed to such a degree that it should now be contraindicated in very young children. The Committee noted that this is the same conclusion that was reached in both the UK and the USA. The Committee noted the Medsafe advice that the use of furosemide oral solution is acceptable if the benefits outweigh the risks for the individual patient. The Committee noted that this view is shared by the European Medicines Agency. The Committee noted that Medsafe considers that the prescribing clinician is in the best position to determine whether the benefits in prescribing furosemide oral solution outweigh the risk of harm for infants under their care. The Committee considered that, in this case, prescribing clinicians did not have alternative options.
- 7.10 The Committee noted the applicant's concerns about the possibility of acute and chronic ethanol toxicity due to the high level of ethanol in the new formulation of Lasix. It was noted that patients unable to take 10 mg doses of furosemide (quarter of a 40 mg tablet) had no alternative treatment option. The Committee noted that the applicant had highlighted that, at this time, there were no ethanol-free formulations of oral-liquid furosemide available and that furosemide tablets are insoluble in water.

- 7.11 The Committee noted that bumetanide tablets and injection, also a loop diuretic, was listed on the Pharmaceutical Schedule. There are also other liquid formulation diuretics listed on the Pharmaceutical Schedule; spironolactone, amiloride and chlorothiazide. However, the Committee considered that these latter would not be suitable funded alternatives in this setting due to their mechanisms of actions and different indications. The Committee noted that furosemide injection is fully funded on the Pharmaceutical Schedule; however, Members considered that it would be difficult to administer small doses to neonates, infants and young children.
- 7.12 The Committee were not aware of any other paediatric furosemide formulations that are ethanol free.
- 7.13 The Committee considered the evidence provided by the applicant and additional references sourced including Zuccotti and Fabiano. (Expert Opin Drug Saf. 2011;10:499-502), Svirskis et al. (Eur J Pediatr 2013. 172:919-26), Marek et al. (Cur Ther Res Clin Exp. 2014;76:90-7), Whittaker et al. (Arch Dis Child. 2009;94:236-40), and Issac et al. (Arch Dis Child. 2013;98: e1).
- 7.14 The Committee noted the narrative review by Marek et al. (Cur Ther Res Clin Exp. 2014;76:90-7) listed a number of oral paediatric prescription and over-the-counter (OTC) pharmaceuticals, in addition to furosemide, which contain ethanol as an excipient. The Committee noted the review was published before the change in ethanol content of furosemide oral liquid. The Committee noted that although the review outlined there were case reports of acute ethanol toxicity in paediatric patients, that none of these cases involved ingestion of oral furosemide. The Committee considered the strength of the evidence to be low.
- 7.15 Members considered that the effects of foetal alcohol syndrome and foetal alcohol effects are well documented, including evidence on how alcohol affects the developing brain. However, Members noted there was no evidence identified that chronic exposure to ethanol as an excipient in prescribed medication leads to potential harm. The Committee considered that, due to a lack of evidence, it was not able to determine the effect of chronic ethanol administration in paediatrics or a safe level of ethanol in oral liquid formulations. However, members considered that, where possible, ethanol use should be avoided in paediatric patients.
- 7.16 The Committee noted the pharmacokinetics of ethanol metabolism. The Committee considered that premature neonates would be at the highest risk of ethanol toxicity due to the immaturity of the developing organs involved in the metabolism of the drug, and would therefore be the patient group with the highest health need. Members noted that premature neonates needing doses less than 5mg would not benefit from the listing of a 20 mg tablet (due to inability to cut a tablet into less than a quarter). The Committee considered that these patients are most at risk of potential harm from ethanol exposure.
- 7.17 The Committee considered that only paediatric patients requiring dosing in 5 mg increments (likely weight range between 5 and 20kg) would benefit from the listing of a 20 mg furosemide tablet.
- 7.18 The Committee considered that ethanol exposure to paediatric patients may cause additional anxiety for carers, particularly in this high-need cardiac surgical setting.
- 7.19 The Committee considered that the estimated patient numbers, 50 patients at any one time, were reasonable, and that the overall budget impact was unlikely to be significant. The Committee considered that should furosemide 20 mg tablets be funded that restrictions would be needed to minimise the risk of use in the adult population, or those who require dosing in greater than 5 mg increments (10 mg and above).

- 7.20 Overall, the Committee considered that furosemide 20 mg tablets should be funded for children with congenital heart disease requiring dosing in 5 mg increments with a high priority, noting the high health need of children with congenital health disease, and the low cost of the treatment.
- 7.21 The Committee considered that PHARMAC should provide the minutes from this discussion to the Medicines Adverse Reactions Committee (MARC), and that PTAC would welcome a response.

8. Anti-VEGF

Anti-VEGF for 2nd line wAMD

Application

- 8.1 The Committee reviewed submissions relating to a proposal to fund ranibizumab second line and aflibercept third line for the use in the treatment of neovascular (wet) aged-related macular degeneration.

Recommendation

- 8.2 The Committee **recommended** that aflibercept be funded as second line anti-VEGF treatment for wAMD after bevacizumab, with a **medium** priority.
- 8.3 The Committee **recommended** that the funding of a third line anti-VEGF agent for wAMD be **declined**.
- 8.4 The Committee **recommended** that the proposed access criteria for second line aflibercept be referred to the Ophthalmology Subcommittee for further development, including objective entry and exit criteria.

Discussion

- 8.5 The Committee noted that in October 2014, the Ophthalmology Subcommittee reviewed aflibercept for the treatment neovascular (wet) age-related macular degeneration (wAMD) and recommended that aflibercept be funded on the HML with a high priority for the second line treatment of wAMD after bevacizumab. The Committee noted that in February 2015 and August 2015 PTAC had recommended that PHARMAC run a Request for Proposal (RFP) process for a second and third line anti-VEGF agent for wAMD.
- 8.6 The Committee noted that in October 2014, the Ophthalmology Subcommittee had also recommended that ranibizumab should be funded as the third line anti-VEGF agent for patients who are of child bearing age or who have had a myocardial infarction (MI) or a stroke within the last three months. The Committee noted that the Subcommittee considered the risk of systemic exposure with ranibizumab to be less than with either bevacizumab or aflibercept.
- 8.7 The Committee noted that in February 2015, PTAC had considered that whilst the Ophthalmology Subcommittee were supportive of aflibercept based in part on clinical opinions that aflibercept may be superior to ranibizumab, there was no evidence available to demonstrate superiority of aflibercept over ranibizumab in wAMD. The Committee noted that in February 2015, PTAC considered that there was no clinical reason not to run a competitive process between aflibercept and ranibizumab for second line treatment of wAMD, and that the Committee would reconsider its view on funding a 3rd line anti-VEGF agent after the competitive process had been run.
- 8.8 The Committee noted that Bayer sent correspondence to PHARMAC in response to the February 2015 PTAC minutes, and that this correspondence was reviewed by PTAC at its August 2015 meeting. The Committee noted that its views, at that time, were unchanged and that PHARMAC should progress with the competitive progress.

- 8.9 The Committee noted in September 2016, PHARMAC consulted on a proposal to fund ranibizumab second line and aflibercept third line for the use in the treatment of wAMD subject to restriction criteria as recommended by the Ophthalmology Subcommittee and PTAC. The Committee noted that consultation feedback included a strong preference from some clinicians for aflibercept to be the second line treatment listed for wAMD, rather than ranibizumab as proposed and that some responders included evidence to support their views that PHARMAC had not previously considered. The Committee noted that following review of all the consultation feedback the PHARMAC Board resolved to not accept any proposal. The Committee noted that PHARMAC was now seeking further advice from PTAC on the issues raised in consultation feedback and any evidence not previously considered.
- 8.10 The Committee noted that past PTAC and Subcommittee meetings have already discussed the health need of wAMD, its epidemiology, risk factors, impact on Māori and other populations, and the availability and suitability of current treatments.
- 8.11 The Committee noted the currently funded treatments listed on the HML for wAMD are intravitreal bevacizumab and intravitreal ranibizumab. Members noted that aflibercept is another anti-VEGF agent with a different molecular structure and mechanism of action to either bevacizumab or ranibizumab in that it binds to both vascular endothelial growth factor-A (VEGF-A), placental growth factor (PlGF), and the anti-angiogenic factor galectin-1. Members considered that the difference in aflibercept's growth factor binding profile gives it a theoretical point of difference compared to the other anti-VEGF agents, bevacizumab and ranibizumab, for ophthalmic use which may partially explain its observed effectiveness when used as an additional line of treatment following those anti-VEGF agents.
- 8.12 [withheld in the interim, pending further clinical review]
- 18.13 The Committee noted the new evidence provided by the supplier of aflibercept, Bayer. The Committee noted the longer-term data from the VIEW1 trial (Kaiser et al 2017, *Ophthalmology Retina*; 1-10) as well as a post-hoc analysis of VIEW1 and VIEW2 trials (Jaffe et al 2016, *Ophthalmology*;123:1856-64). The Committee noted that both the VIEW1 and VIEW2 studies have previously been considered by PTAC, and noted that patients in those trials were treatment naïve, and have different characteristics to the population likely to receive treatment with aflibercept in New Zealand. The Committee therefore considered the applicability and generalisability of those trial results to the New Zealand setting is limited. The Committee noted interim results from two ongoing real world observational studies provided by Bayer (RAINBOW and PERSEUS, unpublished data provided by supplier) which compared the effectiveness and injection frequency with what was observed in the results of the VIEW1 and VIEW2 studies. The Committee noted that these trials were also conducted in treatment naïve patients and therefore considered that their relevance to the New Zealand setting is uncertain.
- 8.14 The Committee noted that there were no high quality, randomised controlled, head-to-head studies looking at the use of aflibercept versus ranibizumab in the second line setting. The Committee noted that, in the New Zealand context, evidence was limited to smaller, lower quality studies looking at the use of ranibizumab and aflibercept in either the second or third line setting.
- 8.15 The Committee reviewed Moisseiev et al 2015 (*RETINA*; 35:1323-30), De Gues et al 2013 (*Acta Ophthalmologica*; 91:411-3), and Kaiser et al 2012 (*Ophthalmic Surg Lasers Imaging*; 43:13-9), which looked at the benefits of ranibizumab in the second line setting after patients had switched from bevacizumab. The Committee noted that both Moisseiev et al (2015) and De Gues et al (2013) were retrospective analyses, where patients who had switched from bevacizumab to ranibizumab were identified and their medical records retrospectively reviewed, and that Kaiser et al was a cohort study. The Committee noted that none of the studies showed a statistically significant change in visual acuity at the

end of follow up after switching to ranibizumab, and that only De Gues et al 2013 showed significant improvements in anatomical changes on optical coherence tomography (OCT), but did not elaborate on what these anatomical changes were.

- 8.16 The Committee noted that there was new evidence published since PTAC's 2015 review on the effects of switching to aflibercept after treatment failure with either bevacizumab, ranibizumab, or both. The Committee noted two meta-analyses, Spooner et al 2017 (Clin Ophthalmol 11:161-77) and Seguin-Greenstein et al 2016 (J Ophthalmol. 2016;4095852) analysing the effectiveness of aflibercept in patients who had switched from bevacizumab and/or ranibizumab. The Committee also noted that Spooner et al (2017) included 28 studies and that Seguin-Greenstein et al (2016) included 7 studies that had also been included in the Spooner et al analysis. The Committee noted that patient baseline characteristics were similar in the Spooner et al meta-analysis. Mean age ranged from 70.1 to 83.4 years, baseline best corrected visual acuity (BCVA) ranged from 42.50 to 74.20 ETDRS letters (a measure of visual acuity which replaces the Snellen and Sloan tests), and the mean central retinal thickness (CRT) ranged from 228.60 to 449.00 μm . The Committee considered that the meta-analysis by Spooner et al (2017) included patients whose eyes had advanced disease and were poor responders to bevacizumab and ranibizumab.
- 8.17 The Committee noted that Spooner et al. (2017) included 19 studies assessing the change in BCVA between baseline and 6 months, and noted that the pooled results found a mean increase of 1.11 letters although this increase was not statistically significant (95% CI -0.25 to 2.46, $P=0.11$). Of the 15 studies included which assessed the change in BCVA over 12 months, a non-significant mean increase of 0.63 letters was found (95% CI -0.26 to 1.52, $P=0.17$). The Committee noted that different treatment regimens had different outcomes in BCVA improvement. In terms of central retinal thickness (CRT), the Committee considered that switching to aflibercept caused a significant reduction in CRT from baseline with a mean reduction of 61.90 μm (95% CI -77.10 to -46.80, $P<0.001$). The Committee considered that anatomical and structural improvements in the eye were associated with the preservation of vision.
- 8.18 The Committee also noted a study by Zhu et al 2016 (Graefes Arch Clin Exp Ophthalmol 255:475-84) assessing the vision-related quality of life in patients treated with 12 months of aflibercept in treatment resistant wAMD. The Committee noted that patient's quality of life (measured using the NEI VFQ-25 composite score) was significantly impacted by changes in the visual acuity score as it affects the patient's ability to be mobile, self-care, and conduct usual daily activities. The Committee however noted that there was no evidence to suggest that structural changes in anatomical central macular thickness alone, would impact quality of life.
- 8.19 [withheld in the interim, pending further clinical review]
- 8.20 The Committee considered that cumulative evidence from first line treatment trials continues to support the notion that bevacizumab, ranibizumab and aflibercept have similar safety and efficacy in wAMD. The Committee considered that there was no robust evidence to support the notion that there would likely be fewer injections (increased time between injections) with aflibercept compared with ranibizumab in the second or third line setting, and that the amount of injections required for both agents was likely to be similar. The Committee highlighted concerns that DHB ophthalmology services are already significantly stretched and that should aflibercept be funded second line, that it is likely that additional resource would be needed.
- 8.21 The Committee considered that whilst the quality of evidence for second line use for both ranibizumab and aflibercept is moderate to poor, both the quantity and quality of evidence is higher for studies using aflibercept than ranibizumab in the second line setting. The Committee considered that given the uncertainty with regards to the therapeutic equivalence of the two agents in the second line setting that it would not be appropriate to

run another RFP for a second line agent in wAMD. The Committee noted that ranibizumab is currently listed in the HML with restrictions, as the second line anti-VEGF agent. The Committee considered that if only one anti-VEGF agent were to be funded for second line treatment, that aflibercept would be the preferred agent. The Committee recommended that aflibercept be funded with a medium priority for use in the second line setting for treatment of wAMD.

- 8.22 The Committee reviewed the recommendation from the 2014 Ophthalmology Subcommittee that depending on the choice of second line anti-VEGF agent, another anti-VEGF agent would be needed for those patients who are pregnant or have recently had a MI or stroke. The Committee considered that there is currently no evidence to support that the risks to pregnant women or patients with a recent myocardial infarction or stroke are different with different anti-VEGF agents. However, the Committee considered that ranibizumab may theoretically be safer in pregnancy than aflibercept and bevacizumab due to the mechanism of action and concerns with systemic absorption, and therefore it may be required for first line anti-VEGF use in this specific patient population. The Committee considered that this patient group (pregnant people requiring a first line treatment) would be likely to be small. With regards to patients who have recently had a MI or stroke the Committee considered that the systemic effects of all anti-VEGF agents are similar, that no one agent is safer than the other. The Committee recommended that funding of a third line agent for wAMD be declined.
- 8.23 The Committee noted the wording of the restriction to the currently listed second line anti-VEGF agent in Section H of the Pharmaceutical Schedule. The Committee noted that the current continuation criteria required patients to re-trial with bevacizumab to demonstrate on-going non-response, and noted that this criterion was recommended previously by the Ophthalmology Subcommittee to help manage fiscal risk. The Committee considered that there is no evidence to support the inclusion of the re-trial criterion. The Committee considered that there should be objective measurements included in the entry criteria, and that exit criteria should also be developed. The Committee considered that the use of visual acuity may provide an objective measure for an exit criterion. The Committee recommended that the Ophthalmology Subcommittee review the restriction for second line anti-VEGF agent, specifically the criteria for re-trial with bevacizumab, and that the Subcommittee develop objective entry and exit criteria.

Ranibizumab for 2nd line DMO

Application

- 8.24 The Committee considered an application from Novartis NZ Limited for the listing of ranibizumab on the Hospital Medicines List (HML) as second line treatment of diabetic macular oedema (DMO) after bevacizumab.

Recommendation

- 8.25 The Committee **recommended** that ranibizumab be listed on the HML as a second line anti-VEGF treatment for diabetic macular oedema with a **low** priority.
- 8.26 The Committee **recommended** that a third line anti-VEGF agent for the treatment of DMO be **declined**.
- 8.27 The Committee **recommended** that the proposed access criteria to second line treatment for DMO be referred to the Ophthalmology Subcommittee for further development, including objective entry and exit criteria.

Discussion

- 8.28 The Committee noted that aflibercept, another anti-VEGF agent, had previously been considered by PTAC for the treatment of diabetic macular oedema (DMO) at its meeting in November 2015, where it was recommended that first line aflibercept for the treatment

of DMO be declined and that the Ophthalmology Subcommittee consider aflibercept as second line anti-VEGF treatment for DMO at its next meeting. The Committee noted the February 2016 Ophthalmology Subcommittee's recommendation where it also recommended that aflibercept for first line anti-VEGF treatment for DMO be declined, and that aflibercept be funded as second line anti-VEGF treatment for DMO with a high priority subject to restrictions.

- 8.29 [withheld in the interim, pending further clinical review]
- 8.30 The Committee noted that uncontrolled DMO eventually leads to blindness, which affects the person's ability to be mobile, self-care, and usual daily activities. Members noted that blind patients will likely require a very high level of carer support for the most basic activities from dressing to cleaning, cooking and feeding. The level of support may reduce over time as the person adapts and learns to cope with blindness. The Committee reviewed a paper by Khan et al 2016 (Adv Med. 2016:4683427) which reported the degree of burden and the proportion at risk for depression among individuals who provide care to visually impaired patients in a Canadian population. The Committee noted that individuals providing care to patients who were legally blind experienced a higher burden than those providing care to patients with low vision (who were not legally blind). In terms of caregiver depression, the Committee noted that there was a 7.45-fold difference in the odds of depression in caregivers who spent >2.5 hours of caregiving compared to those providing <2.5 hours of caregiving. The Committee noted that it was the duration of caregiving, rather than the extent of vision loss which affected the caregivers' risk of depression.
- 8.31 The Committee noted the prevalence of diabetes in Māori, Pacific Island and Indo-Asian populations was 2 to 3 times higher than Europeans, and that Māori had higher rates of diabetic retinopathy and maculopathy compared with non-Māori (Papali'i-Curtin et al, NZ Med J 2013;126:1383-8). The prognosis of these patients was associated with their diabetic control, and a regression of disease was often seen in patients with a reduced HbA1c. The Committee noted the incidence and prevalence of DMO was likely to increase in the future as the number of patients with type 2 diabetes increases. The Committee considered approximately 10% of diabetic patients would develop DMO in their lifetime, and approximately 10% of patients requiring anti-VEGF treatment for centre-involving diabetic macular oedema would not respond to the currently listed first-line agent; bevacizumab.
- 8.32 The Committee noted the currently funded treatments for DMO are laser therapy and intravitreal bevacizumab, which is listed on the HML for ocular neovascularisation or exudative ocular angiopathy. Members noted that laser therapy is effective at preserving vision but less effective at restoring lost vision. Members also noted that the use of bevacizumab in DMO is similar to that in wet age-related macular degeneration (wAMD), in that it is an off-label indication and is often administered using a "treat and extend" protocol where the effect of one intravitreal injection of bevacizumab 1.25 mg can last up to 8 weeks. Members noted that in patients for whom bevacizumab is not considered appropriate e.g. pregnant women or women of child bearing potential, patients with recent MI or stroke; triamcinolone injections were currently being used.

Ranibizumab as 2nd line anti-VEGF for treatment of diabetic macular oedema (DMO)

- 8.33 The Committee noted the evidence provided by Novartis supporting the use of ranibizumab in DMO, and the noted the following phase III trials:
- RESTORE study (Mitchel et al, Ophthalmology 2011;118:615-25) and RESTORE extension study (Lang et al, Ophthalmology 2013;120:2004-12)
 - RETAIN study (Prunte et al, Br J Ophthalmol 2016;100:787-95)

- Diabetic Retinopathy Clinical Research Network (DRCR.net) study (Elman et al, Ophthalmology 2010;117:1064-77)
 - RISE and RIDE studies (Nguyen et al, Ophthalmology 2012;119:789-801) and the long term 36-month results of RISE and RIDE studies (Brown et al, Ophthalmology 2013;120:2013-22)
 - REVEAL study (Ishibashi et al, Ophthalmology 2015;122:1402-15)
- 8.34 The Committee noted that the evidence provided showed that ranibizumab is an effective treatment for DMO in the first line setting versus placebo or laser therapy. However, the Committee considered that the trials had low relevance to the New Zealand setting as patients in New Zealand would have been pre-treated with bevacizumab.
- 8.35 The Committee noted the following papers looking at the effectiveness of ranibizumab after switching from bevacizumab:
- Katz et al. Eur J Ophthalmol 2017;27:210-4.
 - Lee et al. J Ocul Pharmacol Ther 2016;32:659-64.
 - Hanhart et al. Case Rep Ophthalmol 2015;6:44-50.
 - Fechter et al. Ophthalmic Surg Lasers Imaging Retina 2016;47:1030-7
- 8.36 The Committee noted that studies by Katz et al (2017), Lee et al (2016), and Hanhart et al (2015) showed statistically significant improvement in the CRT, but not in visual acuity. The Committee noted Fechter et al (2016), an open-label prospective study evaluating the safety and efficacy of 0.3mg ranibizumab in 30 eyes with DMO after recent, chronic and frequent bevacizumab. In this study the authors reported an overall increase in using Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) score from baseline of +6.5 letters +/- 10.18 (unsure statistical significance) at one year and an overall reduction in central subfield thickness (CST) of -115.57 +/- 136.50 at one year. Members noted that this study also provides evidence that as required (PRN) treatments of ranibizumab are as effective as more frequent injections ('sustained') in the second line context.
- 8.37 The Committee considered that most trials showed that treating with ranibizumab after switching from bevacizumab results in structural improvements, and that only the Fechter et al (2016) study also reported improvements in visual acuity. The Committee considered that both the quality and strength of evidence for second line ranibizumab for DMO was low.
- 8.38 The Committee considered that in patients who do not respond to, or tolerate bevacizumab, that there is an unmet health need for a second line anti-VEGF agent. The Committee considered that ranibizumab may work to address this health need, and recommended that this be funded as second line treatment with a low priority.

Anti-VEGFs for 2nd and 3rd line treatment of DMO

- 8.39 The Committee noted that both aflibercept and ranibizumab are anti-VEGF agents registered for the treatment of DMO. The Committee noted the relative benefit of using either ranibizumab or aflibercept in the second line setting.
- 8.40 The Committee noted the following studies assessing the effectiveness of aflibercept after switching from bevacizumab and/or ranibizumab.
- Bahrami et al, AJO 2016;164:118-27

- Klein et al, Int J Retina Vitreous 2017;3:16
 - Lim et al, Clin Ophthalmol 2015;9:1715-8
 - Mira et al, J Ophthalmol 2017:5632634
- 8.41 Four abstracts from the 2016 Annual meeting of the Associated for Research in Vision and Ophthalmology (ARVO) - Rahimy et al (B0303), Sadowsky et al (B0336), Ores et al (B0339), and Cunningham et al (B0309).
- 8.42 The Committee reviewed a Danish study by Vorum et al (Curr Med Res Opin 2016;32:1943-50) which investigated real world evidence for injection frequency after switching from ranibizumab to aflibercept in DMO and other indications. There was an expectation that the number of injections would reduce due to the perception of prolonged treatment duration with aflibercept. The Committee considered that the study failed to demonstrate a reduction in injection frequency after the switch, and that this finding was consistent with analysis of data reported by Wecker et al (2017) reporting an average of 6 injections of anti-VEGF treatment each year.
- 8.43 The Committee noted that there are no high quality comparative studies available to determine the need, or preferred line of therapy for anti-VEGF treatment in patients with DMO. The Committee noted that there is some level three evidence, from non-experimental studies, suggesting that both ranibizumab and aflibercept provide structural and variable functional benefit in patients resistant to or for whom bevacizumab treatment was failing.
- 8.44 The Committee considered that there is a need for a second line agent in the treatment of DMO but there is not convincing evidence that it should be ranibizumab rather than aflibercept. The Committee considered that from the low quality data available, it is not clear that ranibizumab and aflibercept are therapeutically equivalent in the second line context.
- 8.45 The Committee considered that if there was only one second line agent funded, that there is both more evidence and stronger evidence for aflibercept than ranibizumab. The Committee considered that improvements typically seen with aflibercept were in the third line setting (following bevacizumab and ranibizumab) after ranibizumab has already been trialled and failed, and therefore aflibercept would likely be superior to ranibizumab.
- 8.46 The Committee highlighted concerns that DHB ophthalmology services are already significantly stretched and that should aflibercept be funded second line for DMO that it is likely that additional resource would be needed.
- 8.47 The Committee considered that the evidence for third line anti-VEGF agent for DMO was poor. The Committee recommended that a third line anti-VEGF agent for the treatment of DMO be declined.
- 8.48 The Committee considered that the access criteria previously recommended by the Ophthalmology Subcommittee for aflibercept for DMO would be applicable to either agent for second line use in DMO, however considered these criteria should be developed further to include measures of functional and anatomical benefit from ongoing treatment and an explicit end-point to ensure treatment is not continued when there is only minimal benefit to gain.

9. Tiotropium bromide – severe asthma (resubmission)

Application

- 9.1 The Committee considered a resubmission from Boehringer Ingelheim for widened access to the soft mist form of tiotropium (Spiriva Respimat) for the treatment of severe

asthma in adults who have experienced at least one exacerbation in the previous 12 months while receiving asthma therapy with at least an inhaled corticosteroid (ICS) and a long acting beta2-agonist (LABA).

Recommendation

- 9.2 The Committee **recommended** the application be declined.
- 9.3 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations

Discussion

- 9.4 The Committee noted that it considered an application from Boehringer Ingelheim for the use of the soft mist form of tiotropium (Respimat) for the treatment of severe asthma in adults who meet restriction criteria at its meeting in November 2016 and that it had recommended that the application be declined. The Committee noted that it had previously been unsupportive due to what it considered to be potential safety risks with Respimat being used in a diverse population of COPD patients with many therapeutic options, balanced against the limited evidence of clinical benefits reported by the clinical trials for asthma.
- 9.5 The Committee noted that at its February 2017 meeting it reviewed correspondence received from Boehringer in January 2017 that sought to withhold from publication the entirety of the tiotropium minutes from the November 2016 PTAC meeting as well as additional evidence provided by Boehringer supporting the safety of tiotropium. The Committee noted that at this meeting (February 2017) it had considered that the recommendation to decline the submission was based more on uncertainty around the clinical benefit of tiotropium bromide when used in patients with severe asthma, rather than specifically related to the safety of tiotropium bromide. The Committee noted that at this meeting (February 2017) it had also considered that in the absence of new evidence (other than an editorial by Jenkins, *N Engl J Med* 2013; 369:1555-6) that no amendment or redaction to the minute was necessary.
- 9.6 The Committee noted that the information provided for reconsideration at this meeting (May 2017) was a resubmission of the November 2016 application. The Committee considered that this resubmission was largely the same as what was previously reviewed by PTAC in November 2016 and that the key clinical trials supporting the efficacy of tiotropium when used in the proposed population of adults with severe asthma remain unchanged. The Committee noted the resubmission included the following evidence not previously considered around the safety of tiotropium in asthma and COPD:
- Ducharme et al. *Cochrane Database Syst Rev* 2010 Apr 14;(4)
 - Bateman et al. *J Allergy Clin Immunol* 2015; 136(4):914-22
 - Dahl et al. *Respiratory Medicine* 2016;118: 102-11
 - Halpin et al. *International Journal of COPD* 2015;10:239-59
- 9.7 The Committee noted that at its November 2016 meeting it had reviewed and discussed the following papers regarding efficacy of treatment: Kerstjens et al (*N Engl J Med* 2012;367:1198-207), Ohta et al (*Respirology* 2014;19(supp3):65), Kew et al (*Cochrane Database of Systematic Reviews*, 2016 issue 1.Art.No:CD011721), Price et al (*Asthma Allergy* 2015;8:1-13), NICE 2014 recommendation for tiotropium, GINA (2016) guidelines, and the following papers around the safety of tiotropium in asthma: Wise et al (*N Engl J Med* 2013;369:1491-501), Singh et al (*BMJ* 2011;342:d3215), Chong et al (*Cochrane Database Syst Rev* 2012 Sept 12), and Dong et al (*Thorax* 2013;68:48-56). The Committee considered that it stood by its previous view of the evidence, that whilst an

improvement in FEV1 was shown when tiotropium was added to an ICS/LABA in the treatment of patients with severe asthma, the change in FEV1 was substantially less than what had been shown to be the minimal patient perceived difference, that improvements in the patient outcome Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores did not achieve minimal clinically important differences, and that the confidence interval for the change in the frequency and number of exacerbations do not rule out no effect.

- 9.8 The Committee reviewed Ducharme et al 2010 (Cochrane Database Syst Rev 2010 Apr 14;(4)), a systematic review and meta-analysis of randomised control trials where inhaled long acting beta agonists (LABAs) were added to ICS in adults and children over 2 years of age with asthma. The authors found 77 studies which met the meta-analysis' eligibility criteria measuring 21,248 trial participants in total. The study participants were noted to be generally symptomatic at baseline with moderate airway obstruction despite their current ICS regimen. The Committee noted that the addition of a LABA to an ICS lead to a modest improvement in FEV1 of 110 mL (95% CI: 90 mL to 130 mL), however noted that the authors did not comment on whether this increase in FEV1 was considered clinically significant or meaningful.
- 9.9 The Committee reviewed the results of Bateman et al (J Allergy Clin Immunol 2015; 136(4):914-22), a systematic review and network meta-analysis indirect comparison that examined the magnitude of response in randomised, double blinded clinical trials of commonly used asthma drugs when measured with the ACQ-7 and/or AQLQ instruments and whether the treatments exceeded the minimally important difference (MID) as measured using those tools. The authors identified 64 randomised controlled trials for inclusion into this meta-analysis, of which 54 trials used the AQLQ and 11 used the ACQ instrument (1 trial using both). The Committee noted that when compared with placebo, only an ICS with or without a LABA achieved the minimally important difference using either the AQLQ or ACQ or both. The Committee noted the authors' view that future studies should employ methods that reduce the placebo effect seen in patients receiving an ICS as background treatment, and that for most treatments, particularly when asthma therapies are combined, the mean difference between treatment groups exceeding the MID is probably not achievable. The Committee noted that only 11 papers out of 64 included in this study used the ACQ, being the quality of life instrument that was used in Kerstjens 2012, and considered that the results of this paper (Bateman et al 2015) may not be generally applicable to ACQ.
- 9.10 The Committee noted Boehringer's comments about the Santanello et al 1999 (Eur Respir J; 14:23-7), a trial which PTAC had referenced at its November 2016 meeting, describing the relationship between the minimally perceived patient improvement and changes to FEV1. The Committee further noted the comments that patients in the Santanello trial had different baseline characteristics to patients that tiotropium is intended to treat. The Committee however considered that, from the literature available, there is no evidence to suggest that a smaller improvement in FEV1 than what was observed in the Santanello trial, albeit in more heavily treated patients, would influence the patient's perception of benefit.
- 9.11 The Committee considered that the new information provided by Boehringer in the resubmission did not change PTAC's previous view that the evidence for the clinical benefit with add-on tiotropium is limited and uncertain.
- 9.12 In terms of safety, the Committee reviewed Dahl et al 2016 (Resp Med;118:102-11) and Halpin et al, 2015 (Int J COPD;10:239-59), which pooled safety data from tiotropium asthma and COPD trials respectively, to evaluate the safety and tolerability of tiotropium solution for inhalation delivered via the Respimat device.
- 9.13 The Committee noted that Dahl et al 2016 (Resp Med 2016;118:102-11) used pooled safety data from seven phase II and phase III, randomised, double blind, parallel group

trials, which investigated once-daily tiotropium Respimat (5 mcg or 2.5 mcg) versus placebo as add-on treatment to different levels of background maintenance therapy, including at least ICS. The exclusion criteria were similar across all seven trials with regards to respiratory and cardiac co-morbidities. The Committee noted that the proportions of patients with adverse events (AEs) were comparable between treatment groups: tiotropium 5 mcg at 60.8%, placebo 5 mcg pool at 62.5%, tiotropium 2.5 mcg at 57.1%, placebo 2.5 mcg pool at 55.1% and that the proportions of cardiac AEs were comparable between tiotropium and placebo: tiotropium 5 mcg at 1.4%, placebo 5 mcg pool at 1.4%, tiotropium 2.5 mcg at 1.4%, placebo 2.5 mcg pool at 1.15%. The most common cardiac AEs were palpitations and tachycardia, none of which were reported in more than 0.5% of patients in any treatment arm. The Committee noted that the proportions of patients with serious AEs were balanced across groups: tiotropium 5 mcg at 4.0%, placebo 5 mcg pool at 4.9%, tiotropium 2.5 mcg at 2.0%, placebo 2.5 mcg pool at 3.3%. The Committee noted that the most frequent AEs reported were asthma, decreased peak expiratory flow rate and nasopharyngitis.

- 9.14 The Committee noted Halpin et al 2015 (Int J COPD;10:239-59), a pooled safety analysis from 35 randomised, double blind, parallel group, placebo controlled, clinical trials in patients with COPD (28 HandiHaler, and 7 Respimat), which studied adverse event rates for tiotropium dry powder for inhalation (HandiHaler) and tiotropium solution for inhalation (Respimat). The Committee noted that the included trials used similar inclusion and exclusion criteria. The Committee noted that with regards to cardiac comorbidities in the exclusion criteria, earlier trial protocols had heart failure resulting in hospitalisation in the previous 3 years, cardiac arrhythmia requiring drug treatment, or myocardial infarction (MI) within the past year as exclusion criteria. Other than these specific criteria, heart failure and ischemic heart disease were not excluded. The Committee noted that more recent trials used less stringent exclusion criteria, such as life-threatening cardiac arrhythmia or arrhythmia requiring a change in medication within the last year, heart failure resulting in hospitalisation in the past year, and/or MI within the preceding 6 months.
- 9.15 [withheld in the interim, pending further clinical review]
- 9.16 [withheld in the interim, pending further clinical review]
- 9.17 [withheld in the interim, pending further clinical review]
- 9.18 The Committee noted the current New Zealand Adult Asthma Guidelines (Beasley et al. NZMJ 2016) do not recommend tiotropium as an add-on treatment for severe asthma. The Committee considered that single inhaler maintenance and reliever therapy (SMART) should be the treatment against which add-on tiotropium should be compared with, and that the evidence provided does not show improved patient outcomes with add-on tiotropium. The Committee considered that patients with asthma in New Zealand currently have a range of treatment options available and that improved prescribing, health literacy, and adherence to currently available medicines would significantly improve asthma patient outcomes. The Committee considered that the evidence provided in the resubmission did not sufficiently address the uncertainties of clinical benefit and if anything raised more concerns around the safety of tiotropium in COPD.
- 9.19 The Committee considered that its previous recommendation to decline stands.

10 Secukinumab – Severe plaque psoriasis

Application

- 10.1 The Committee considered a funding application from Novartis New Zealand Limited (Novartis) for a new listing of secukinumab subcutaneous injections for severe chronic plaque psoriasis in the Pharmaceutical Schedule.

Recommendations

- 10.2 The Committee **recommended** that secukinumab for the treatment of severe chronic plaque psoriasis be funded with a **medium** priority.
- 10.3 The Committee **recommended** that the funding application be referred to the Dermatology Subcommittee for further advice, particularly on whether the proposed Special Authority criteria should include the Dermatology Quality of Life Index (DLQI) in addition to the currently used Psoriasis Area Severity Index (PASI) assessment.
- 10.4 The Committee **recommended** advice be sought from the Dermatology Subcommittee as to whether there is a place in having anti-TNF biologics as the first-line biologic, and non-anti-TNF biologics (such as secukinumab) as a second-line biologic.
- 10.5 The Committee took into account PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 10.6 The Committee noted that psoriasis is a polygenic, multifactorial disease of the skin. Chronic plaque psoriasis is the most common variant of psoriasis, accounting for about 79% of cases in adults. The Committee noted that the prevalence of chronic plaque psoriasis in Māori was comparable with non- Māori.
- 10.7 The Committee noted that heart disease, psoriatic arthritis, diabetes, and depression are common comorbidities that add to the burden of disease. In those with moderate/severe disease, there is a quality of life reduction that is comparable with diabetes, myocardial infarction and some cancers.
- 10.8 The Committee noted that in clinical trials, the measure of overall psoriasis severity and coverage is the Psoriasis Area Severity Index (PASI) assessment. Severe psoriasis is now defined as PASI > 10 (previously > 15) and the target for treatment is defined as a maintained change in PASI ≥ 75% improvement (PASI 75). The Committee noted that in the more recent trials with new non-TNF biologics, the numbers of participants achieving higher PASI reductions, including a 90% reduction (PASI 90) and total clearance (PASI 100), have been increasing.
- 10.9 The Committee noted that the Dermatology Quality of Life Index (DLQI) is an assessment using 10 questions (score 0 to 30) to measure the impact of skin disease on the patient. The Committee noted that this measure is in use internationally and considered relevant in determining psoriasis severity. DLQI is used in the Australian treatment consensus guidelines (Baker et al. Australas J Dermatol. 2013;54:148-54) and in the UK NICE Guideline (<https://www.nice.org.uk/guidance/ta350>). The Committee noted that a reduction in DLQI score of at least 4-5 in response to treatment would be considered clinically significant (Khilji et al. Br J Dermatol 2002;147(Suppl 2):50).
- 10.10 The Committee noted current first-line treatments in New Zealand are topical pharmaceuticals including moisturisers, corticosteroids, vitamin D analogues, coal tar and salicylic acid. Second-line treatments are phototherapy (if available), acitretin, methotrexate and ciclosporin. Third-line treatments are anti-TNF biologics, particularly adalimumab, occasionally etanercept, and rarely infliximab.
- 10.11 The Committee noted secukinumab is a fully human monoclonal IgG1κ antibody that binds specifically to IL-17A and this novel mechanism of action differs to that of other biologics used for plaque psoriasis. It is produced in Chinese hamster ovary cells using recombinant DNA technology.
- 10.12 The Committee noted that the safety and efficacy of secukinumab were evaluated versus placebo or etanercept in four randomised, double-blind, placebo-controlled phase 3 studies (FEATURE, JUNCTURE, ERASURE and FIXTURE) in adult patients with

moderate to severe chronic plaque-type psoriasis poorly controlled by topical treatments and/or phototherapy and/or systemic therapy.

- 10.13 The Committee noted the FEATURE study (Blauvelt et al. *Br J Dermatol.* 2015;172:484-93) in 177 patients randomised in a 1:1:1 ratio to secukinumab 150 mg or 300 mg or placebo for 12-weeks. PASI 75 response rates were 75.9% for secukinumab 300 mg, 69.5% for secukinumab 150 mg, and 0% for placebo at week 12 ($p<0.0001$).
- 10.14 The Committee noted the JUNCTURE study (Paul et al. *J Eur Acad Dermatol Venereol.* 2015;29:1082-90) in 182 patients randomised in a 1:1:1 ratio to secukinumab 150 mg, secukinumab 300 mg or placebo for 12 weeks. PASI 75 response rates were 86.7% for secukinumab 300 mg, 71.7% for secukinumab 150 mg, and 3.3% for placebo at week 12 ($p<0.0001$). The study continued with maintenance treatment up to Week 52, a treatment extension up to Week 208 and an 8-week treatment-free follow-up period.
- 10.15 The Committee noted the ERASURE study (Langley et al. *N Engl J Med.* 2014;371:326-38) in 738 patients randomised in a 1:1:1 ratio to secukinumab 150 mg, secukinumab 300 mg or placebo for 52-weeks. The Committee noted at week 12, the primary endpoint of PASI 75 was achieved by 81.6% of patients treated with 300 mg secukinumab and 71.6% of patients treated with 150 mg secukinumab, compared with 4.5% of patients receiving placebo ($p<0.001$ for each secukinumab dose vs. comparators). Both the 300 mg dose and 150 mg dose of secukinumab were superior to placebo in terms of PASI 90 response at week 12 ($p<0.001$ for both comparisons). A total of 59.2% of patients treated with secukinumab 300 mg achieved PASI 90, compared with 39.1% for secukinumab 150 mg, and 1.2% for placebo. The Committee noted the ERASURE trial also showed an improvement in DLQI to 0 or 1 as early as week 4 in 46% of patients in the secukinumab 300 mg group compared to 25% in the secukinumab 150 mg group and 13.8% in placebo group ($p<0.01$).
- 10.16 The Committee noted the FIXTURE study (Langley et al. *N Engl J Med.* 2014;371:326-38) in 1306 patients randomised in a 1:1:1:1 ratio to secukinumab 150 mg, secukinumab 300 mg, etanercept or placebo for 52-weeks. The Committee noted at week 12, the primary endpoint of PASI 75 was achieved by 77.1% of patients treated with 300 mg secukinumab and 67% of patients treated with 150 mg secukinumab, compared with 44% of patients receiving etanercept and 4.5% of patients receiving placebo ($p<0.001$ for each secukinumab dose vs. comparators). Both the 300 mg dose and 150 mg dose of secukinumab were superior to placebo in terms of PASI 90 response at week 12 ($p<0.001$ for both comparisons). A total of 54.2% of patients treated with secukinumab 300 mg achieved PASI 90, compared with 41.9% for secukinumab 150 mg, 20.7% with etanercept and 1.2% for placebo. The Committee noted the FIXTURE trial showed a statistically significant decrease in DLQI by week 12 in a higher proportion of secukinumab patients compared to etanercept and placebo groups ($p<0.001$).
- 10.17 The Committee considered all four placebo-controlled trials were company sponsored but were also of good quality with, participants appropriately randomised and allocated to treatment, and baseline demographics and disease characteristics were balanced across intervention groups. The Committee considered there is strong evidence that secukinumab 300 mg and secukinumab 150 mg is superior to placebo for PASI efficacy outcomes at week 12 and 52.
- 10.18 The Committee noted that dermatology life quality index (DLQI) score was assessed in all four placebo-controlled trials. In all the trials, secukinumab improved (that is, reduced) DLQI score at week 12 from baseline by between 10.4 to 11.6 points, which was higher than with placebo (1.1 to 1.9 points; $p<0.001$ for all trials other than FIXTURE, in which no p value was given). The number of people with a week 12 DLQI of 0 or 1 (that is, showing no impact on daily living) was statistically significantly higher for secukinumab in all trials than with placebo ($p<0.001$) and etanercept ($p<0.001$).

- 10.19 The Committee noted the CLEAR study of secukinumab versus ustekinumab (Blauvelt et al. *J Am Acad Dermatol.* 2017;76:60-9) trial demonstrated an improved DLQI in a greater proportion of patients at all time points up to week 16 in the secukinumab 300 mg group compared to the ustekinumab group. In addition, the CLEAR trial also used a subjective symptom assessment to evaluate pain, itching, and scaling on an eleven-point scale with a higher score signifying worsening symptoms. The secukinumab group achieved lower scores in pain, itching, and scaling when compared to the ustekinumab group.
- 10.20 The Committee noted the SCULPTURE study of retreatment-as-needed versus a fixed-interval regimen (Mrowietz et al. *J Am Acad Dermatol.* 2015;73:27-36). Participants completed 12 weeks of secukinumab 150 or 300 mg, then those patients who achieved PASI 75 were rerandomized to secukinumab retreatment as needed (n = 217, 300 mg; n = 206, 150 mg) or fixed interval retreatment. (n = 217; n = 203). More patients on fixed interval retreatment (78.2%, 300 mg; 62.1%, 150 mg) maintained PASI 75 versus retreatment as needed (67.7%; 52.4%).
- 10.21 The Committee noted there were no head-to-head trials available comparing secukinumab to adalimumab, which was the most appropriate comparator in New Zealand. The Committee considered that secukinumab was likely superior in terms of efficacy compared to adalimumab based on rates of achievement of PASI 75 and PASI 90 in the clinical trials. The Committee considered secukinumab could replace adalimumab if funded with the same criteria.
- 10.22 The Committee considered that the safety data for secukinumab is comparable with available biologics. Specific safety concerns for the use of secukinumab include its use in patients with inflammatory bowel disease (where Crohn disease may worsen); reversible transient neutropenia; patients with a latex allergy; and the occurrence of mild to moderate oral or genital candidiasis (Xiong et al. *Int J Clin Exp Med.* 2015;8:3156–72).
- 10.23 The Committee noted that psoriasis biologic registries have reported the median drug survival (or persistence of effect) for the anti-TNF agents is approximately four years, possibly due to the development of anti-drug antibodies. The Committee noted there was currently insufficient long term data to determine the drug survivability of secukinumab.
- 10.24 The Committee considered the patient population that would benefit most from secukinumab are those with a PASI >10 with DLQI >10 and failure of an adequate trial of three of the following four treatments: phototherapy, acitretin, methotrexate and ciclosporin. The Committee noted this differed from the current access to adalimumab and thus recommended advice be sought from the Dermatology Subcommittee on this aspect.
- 10.25 The Committee also recommended advice be sought from the Dermatology Subcommittee as to whether there is a place in having anti-TNF biologics as the first-line biologic, and non-anti-TNF biologics such as secukinumab, as a second-line biologic.
- 10.26 The Committee noted that secukinumab may result in faster response times than alternatives, including anti-TNF biologics, although the Committee considered that in the context of severe plaque psoriasis as a chronic disease, this was not so clinically important.
- 10.27 The Committee noted that secukinumab maintenance involved monthly injections, which was less frequent administration than fortnightly adalimumab or twice weekly etanercept.