

## **PTAC meeting held on 5 & 6 May 2016**

### **(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.

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## **1. Subcommittee Minutes**

### ***Reproductive and Sexual Health Subcommittee***

- 1.1. The Committee noted and accepted the minutes from the Reproductive and Sexual Health Subcommittee teleconference of 19 October 2015.

### ***Endocrinology Subcommittee***

- 1.2. The Committee noted and accepted the minutes from the Endocrinology Subcommittee teleconference of 27 January 2016.

### ***Haematology Subcommittee***

- 1.3. The Committee noted and accepted the minutes from the Haematology Subcommittee meeting of 16 March 2016.
- 1.4. The Committee noted that PHARMAC was considering potential future funding options for novel oral anticoagulants (NOACs), with one option being the release of a competitive process for NOACs. The Committee requested that PHARMAC keep the Committee informed if any changes to the funded NOACs were proposed as a result of such a process.
- 1.5. Members considered that based on their clinical experience, the rate of gastrointestinal discomfort associated with dabigatran is significant and this may lead to poor adherence in a number of patients.

### ***Analgesic Subcommittee***

- 1.6. The Committee noted and accepted the minutes from the Analgesic Subcommittee meeting of 1 March 2016.
- 1.7. The Committee supported the Analgesic Subcommittee's recommendation that PHARMAC delist tramadol oral drops 100 mg/ml from the HML for safety reasons.
- 1.8. The Committee supported the Analgesic Subcommittee's recommendation that PHARMAC include a reminder within the online NPPA application process for clinicians to seek patient consent. The Committee noted the additional administration required but agreed the online form should be consistent.

### ***Dermatology Subcommittee***

- 1.9. The Committee noted the record of the Dermatology Subcommittee of PTAC meeting held on 30 November 2015.
- 1.10. The Committee accepted the recommendations made by the Subcommittee with the exception of recommendations made in paragraphs 4.6, 4.23, 5.10, 5.16, 5.5, 5.31, 5.39, 9.2, 11.3
- 1.11. The Committee noted the minute on paragraph 4.6 and gave the recommendation a Medium priority.
- 1.12. The Committee noted that, in paragraph 4.23 the issue had been resolved as a less expensive and equally effective compounded terbinafine oral solution is funded.
- 1.13. The Committee noted the minute on paragraph 5.10 was not required. Members noted the Tender Medical Evaluation Subcommittee already takes this into account during its evaluation, and PHARMAC communicates the preference for creams to come in pumps to suppliers when bidding in the annual tender.

- 1.14. The Committee noted the minute on paragraph 5.16 and considered this recommendation was difficult to implement and it was not PHARMAC's position to direct clinical practice. Members noted PHARMAC should work with professional bodies to increase prescriber, pharmacist and patient awareness of topical corticosteroid strength.
- 1.15. The Committee noted that, in paragraph 5.5, the treatment algorithm on acne had changed since the original recommendation was made by the Dermatological Subcommittee. Members considered a funding application on topical benzyl peroxide for the treatment of acne should be brought to the Committee for its review.
- 1.16. The Committee noted the wording on paragraph 5.31 and considered the wording of "BPAC article" should reflect "educational article".
- 1.17. The Committee noted the minute on paragraph 5.39 on sodium hypochlorite and disagreed with the recommendation. The Committee considered simple bleach could be bought for a lower price than the co-payment.
- 1.18. The Committee noted the minute on 9.1 and agreed with the subcommittee's recommendation on topical antibiotics. The Committee noted this recommendation was in line with the minutes from the last Anti-infective subcommittee and did not need to go back for review. The Committee gave the recommendation a High Priority.
- 1.19. The Committee noted the minute on paragraph 9.2 and gave the recommendation a High priority.
- 1.20. The Committee noted the minute on paragraph 11.3 and considered it was part of PHARMAC's work on devices and medicines.

### ***Ophthalmology Subcommittee***

- 1.21. The Committee noted the record of the Ophthalmology Subcommittee of PTAC meeting held on 24 February 2016.
- 1.22. The Committee accepted the recommendations made with the exception of recommendations made in paragraphs 3.17, 3.24, 4.3, 5.3, and 7.5.
- 1.23. The Committee noted that, in paragraph 3.24, the Subcommittee recommended that PHARMAC seek an alternative supplier for prednisolone acetate eye drops, or a generic supply, while researching what other countries were using in place of Pred Mild and what evidence was available for other agents. The Committee considered this recommendation could not be progressed as there were no alternatives suppliers for low strength prednisolone eye drops.
- 1.24. The Committee noted the wording of paragraph 3.17 and 4.3, and as considered the wording of "BPAC article" should reflect "educational article".
- 1.25. The Committee noted that, in paragraph 5.3, the Subcommittee recommended that ciclosporin 0.05% eye preparation be funded on the Pharmaceutical Schedule for the treatment of vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and the treatment of dry eye disease, secondary to secretive dysfunction. Members considered the Committee should review the evidence for severe keratoconjunctivitis sicca at a future PTAC meeting.
- 1.26. The Committee noted paragraph 7.5, relating to low-dose atropine therapy for myopia prevention and recommended Subcommittee members work with RANZCO and PHARMAC staff to submit a funding application. The Committee requested it review such a submission at a future PTAC meeting.

## **2. Correspondence**

### ***Aflibercept***

- 2.1. The Committee noted correspondence from Bayer New Zealand Ltd in response to PTAC's November 2015 meeting minutes for aflibercept for the treatment of diabetic macular oedema.
- 2.2. The Committee acknowledged the correspondence from Bayer and thanked the supplier for their letter.

### ***Rivaroxaban***

- 2.3. The Committee noted correspondence from a clinical pharmacist requesting that PTAC reconsider its funding recommendation from its May 2014 meeting that gave higher funding priority to apixaban over rivaroxaban as anticoagulation for stroke prevention in atrial fibrillation.
- 2.4. The Committee noted this correspondence had been considered by the Haematology Subcommittee as part of their advice to PHARMAC on novel oral anticoagulants (NOACs). The Committee considered that this was appropriate and no changes to their earlier recommendations were required at this time.

### ***Moxifloxacin***

- 2.5. The Committee noted correspondence from the Canterbury DHB Antimicrobial Stewardship Committee in response to PTAC's Anti-Infective Subcommittee November 2015 meeting minutes and PTAC's February 2016 meeting minutes for moxifloxacin for penicillin allergic patients post splenectomy. The correspondence requested consideration of wider access for prescribing; citing access to immunologists and dermatologists being a concern. Canterbury DHB Antimicrobial Stewardship Committee also requested reconsideration of access to moxifloxacin for this indication via Section B of the Pharmaceutical Schedule.
- 2.6. The Committee raised concerns around the ability to diagnose dermatological conditions and potential for over-diagnosis.
- 2.7. The Committee considered that there may be poor physical access in some areas to dermatologists and immunologists. However, the Committee noted that physical access may be overcome through teledermatology, and that an image can easily be sent securely to a dermatologist or immunologist to confirm the diagnosis.
- 2.8. The Committee considered the restrictions recommended were not to facilitate skin prick testing; rather, to maintain anti-microbial stewardship via securing an accurate diagnosis of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (TEN), or a confirmed immediate hypersensitivity to penicillin.
- 2.9. The Committee noted the Anti-Infective Subcommittee's previous recommendation that access to moxifloxacin for this indication should be limited to Section H of the Pharmaceutical Schedule and should not be listed in the community. The Committee noted that it had ratified this minute at its February 2016 meeting. The Committee considered that this was appropriate and re-iterated its recommendation that moxifloxacin should only be available for penicillin allergic patients post splenectomy in Section H of the Pharmaceutical Schedule.

### ***Crizotinib***

- 2.10. The Committee noted correspondence from Pfizer New Zealand Limited in response to the November 2015 PTAC minute for crizotinib for the treatment of anaplastic lymphoma kinase (ALK) positive advanced and/or metastatic non-small cell lung cancer (NSCLC) in first and second-line settings.

- 2.11. The Committee reiterated its previous recommendations to decline applications for crizotinib as a first and second-line treatment for ALK positive advanced and metastatic NSCLC.
- 2.12. The Committee noted its previous recommendation that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) for consideration. The Committee noted that this was planned to occur at the next meeting of CaTSoP and that Pfizer's correspondence would be included in the material presented to the Subcommittee.

#### ***Ibrutinib***

- 2.13. The Committee noted correspondence from Janssen-Cilag in relation to the November 2015 PTAC minute for ibrutinib for the treatment of chronic lymphocytic leukaemia (CLL) and mantle cell leukaemia (MCL).
- 2.14. The Committee noted correspondence from Janssen-Cilag in relation to the recently released National Institute for Health and Care Excellence (NICE) Appraisal Consultation Document regarding ibrutinib.
- 2.15. The Committee noted correspondence from haematologists from the Midland region, haematologists from the Southern DHB, a haematologist from North Shore Hospital, a haematologist from Capital and Coast DHB, and Leukaemia and Blood Cancer New Zealand in relation to the November 2015 PTAC minute for ibrutinib for the treatment of CLL and MCL.
- 2.16. The Committee noted the concerns raised, and clarified that its comments about the need for longer-term data in a long-term condition related to CLL in general, not high-risk CLL specifically which the Committee agreed has a different disease course.
- 2.17. The Committee considered that funding applications should demonstrate the benefit of the requested treatment in a New Zealand setting. The Committee considered that there are difficulties in assessment of benefit in situations without direct comparisons and noted that this was reflected in international material.
- 2.18. The Committee noted that the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia did not recommend that ibrutinib be funded for the treatment of CLL noting that the patient population and clinical place of ibrutinib were not adequately defined, the size of the comparative clinical benefit could not be quantified, and the cost effectiveness and financial implications were underestimated and unacceptably high.
- 2.19. The Committee noted that NICE did not recommend ibrutinib for the treatment of CLL noting that immaturity of the data and an uncertain and unfavourable cost-effectiveness.
- 2.20. The Committee reiterated its previous recommendation that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) for consideration and advice regarding CLL treatment in New Zealand. The Committee noted that an updated submission had been provided by the applicant for consideration by CaTSoP, which is due to occur in the near future. The Committee noted that all correspondence relating to ibrutinib would be included in the material presented to the Subcommittee.

### **3. Nivolumab for locally advanced or metastatic non-small cell lung cancer Application**

- 3.1. The Committee considered an application from Bristol-Myers Squibb (NZ) Ltd (BMS) for the funding of nivolumab (Opdivo) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) for patients who have progressed on or after prior platinum-based chemotherapy.

## **Recommendation**

- 3.2. The Committee **recommended** that nivolumab as monotherapy be funded with a low priority for the treatment of patients with locally advanced or metastatic squamous and nonsquamous NSCLC that has progressed on or after prior platinum-based chemotherapy, subject to the following Special Authority criteria:

Nivolumab—PCT only - Specialist  
Special Authority for Subsidy

**Initial Application** — only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:

**All of the following:**

- 1.1 Patient has locally advanced or metastatic non-small cell lung cancer; and
- 2.1 Patient has documented disease progression following treatment with platinum based chemotherapy; and
- 3.1 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

**Renewal application** — only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:

**All of the following:**

- 1.1 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks; and
- 2.1 No evidence of progressive disease according to RECIST criteria; and
- 3.1 The treatment remains clinically appropriate and the patient is benefitting from treatment and tolerating treatment.

- 3.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

## **Discussion**

- 3.4. The Committee noted that lung cancer was the fifth most common cancer registered in New Zealand in 2012, accounting for 9% of all registrations. The Committee noted that lung cancer was the leading cause of cancer death in 2012, accounting for 19% of all cancer deaths and a third of all Maori cancer deaths (Ministry of Health. 2012. Cancer: New registrations and deaths 2012)
- 3.5. The Committee noted that NSCLC is the most common type of lung cancer with the majority of patients presenting with advanced stage IIIB or IV disease at diagnosis. The Committee noted that survival rates for patients with advanced disease are poor with currently funded treatment options; the 1-year survival for patients with stage IV disease treated with chemotherapy is 10%. The Committee considered patients with locally advanced or metastatic NSCLC had a high health need.
- 3.6. The Committee noted that for patients with advanced non-resectable nonsquamous NSCLC who have tested positive for epidermal growth factor receptor (EGFR) tyrosine kinase activating mutations the current standard first-line treatment is with tyrosine kinase inhibitors erlotinib (Tarceva) or gefitinib (Iressa). The Committee noted for patients with advanced non-resectable EGFR-negative NSCLC and squamous NSCLC the current standard first-line treatment is with platinum-based chemotherapy.
- 3.7. The Committee noted that for patients who progress on or after first-line treatment, platinum-based chemotherapy for EGFR positive patients or docetaxel for all other patients are the currently funded standard second-line treatment options.
- 3.8. The Committee noted that nivolumab is a fully human IgG4 monoclonal antibody immune checkpoint programmed cell death (PD)-1 inhibitor. The Committee noted that PD-1 is a protein expressed on T-cells that transmits co-inhibitory signals upon engagement with the tumour-expressed ligands PD-L1 and PD-L2. The Committee noted that the PD-1 system is pivotal in the regulation of autoimmunity, transplantation immunity, infectious immunity, and tumour immunity.

- 3.9. The Committee noted that the recommended dose of nivolumab for the treatment of locally advanced or metastatic NSCLC is 3 mg/kg as monotherapy administered intravenously over 60 minutes every 2 weeks, continued as long as clinical benefit is observed or the treatment is no longer tolerated.

#### *Squamous NSCLC*

- 3.10. The Committee noted that the key evidence for nivolumab for the treatment of squamous NSCLC comes from CHECKMATE-017 (CA209-017). This was a randomised, open-label, international phase III study of nivolumab compared with docetaxel in 272 patients with stage IIIb or IV squamous cell NSCLC who had disease recurrence after one prior platinum-containing regimen (Brahmer et al. N Eng J Med 2015;373:123-135).
- 3.11. The Committee noted that patients were randomised to receive either nivolumab (3 mg/kg every 2 weeks, n=135) or docetaxel (75 mg/m<sup>2</sup> every 3 weeks, n=137) until disease progression or discontinuation due to toxic effects or other reasons.
- 3.12. The Committee noted that at the time of database lock on 15 December 2014, 199 of the 272 patients had died. The Committee noted that median overall survival (OS), the primary endpoint of the study, was 9.2 months (95% CI, 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel (HR for death 0.59; 95% CI 0.44 to 0.79; p<0.001). The Committee considered that the benefit of nivolumab was limited with an OS gain of 3.2 months based on a small number of patients remaining on treatment. The Committee considered that with longer follow-up, it was possible that nivolumab's benefit would be better demonstrated.
- 3.13. The Committee noted that the reported response rate was 20% (95% CI 14 to 28) with nivolumab versus 9% with docetaxel (95% CI 5 to 15; p=0.008) and the median progression-free survival (PFS) was 3.5 months (95% CI, 2.1 to 4.9) with nivolumab versus 2.8 months (95% CI, 2.1 to 3.5) with docetaxel (HR for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; p<0.001).
- 3.14. The Committee noted that the most frequent reported treatment-related grade 3 or 4 adverse events in the docetaxel group were neutropenia (30%), fatigue (8%) and febrile neutropenia (10%) and that no grade 4 adverse events were reported in the nivolumab group and three treatment related grade 3 adverse events were reported, one case each of tubulointerstitial nephritis, colitis and pneumonitis.

#### *Nonsquamous NSCLC*

- 3.15. The Committee noted that the key evidence for nivolumab for the treatment of nonsquamous NSCLC comes from CHECKMATE-057 (CA209-057). This was a randomised, open-label, international phase III study of nivolumab in comparison with docetaxel in 582 patients with stage IIIb or IV or recurrent nonsquamous NSCLC after radiation therapy or surgical resection and disease progression during or after one prior platinum-based doublet chemotherapy regimen (Borghaei et al N Eng J Med 2015;373:1627-39).
- 3.16. The Committee noted that patients were randomised to receive either nivolumab (3 mg/kg every 2 weeks, n=292) or docetaxel (75 mg/m<sup>2</sup> every 3 weeks, n=290) until disease progression or discontinuation due to toxicity or other reasons.
- 3.17. The Committee noted that enrolled patients with known EGFR mutation or anaplastic lymphoma kinase translocation were allowed to have received or be receiving an additional line of tyrosine kinase inhibitor therapy, and a continuation of or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib was allowed in all patients. The Committee noted that exclusion criteria included prior treatment with immune-stimulatory anti-tumour agents including checkpoint-targeted agents, or prior docetaxel therapy.

- 3.18. The Committee noted that at a minimum follow up of 13.2 months, median OS, the primary end-point of the study, was reported to be 12.2 months (95% CI, 9.7 to 15.0) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel (HR for death, 0.73; 96% CI, 0.59 to 0.89; p=0.002). The Committee noted that at one year the OS rate was 51% (95% CI, 45 to 56) with nivolumab and 39% (95% CI, 33 to 45) with docetaxel. The Committee noted that the overall response rate (ORR) was 19% with nivolumab versus 12% with docetaxel (p=0.02).
- 3.19. The Committee noted that 24% of patients in the nivolumab arm continued treatment beyond initial disease progression, of whom 23% had a nonconventional pattern of benefit. Members considered that in future New Zealand clinical practice may be to discontinue immune based treatments for patients with disease progression.
- 3.20. The Committee noted that grade 3 or 4 treatment-related adverse events were reported in 10% of patients in the nivolumab arm and 54% in the docetaxel arm. The Committee noted that the most frequently reported adverse events of any grade in the nivolumab arm were fatigue (16%), nausea (12%), decreased appetite (10%) and asthenia (10%) and in the docetaxel arm the most frequently reported adverse events of any grade were neutropenia (31%), fatigue (29%), nausea (26%) and alopecia (25%).
- 3.21. The Committee noted that the published Kaplan Meier survival curves crossed over and considered that, in general, statistical assumptions about hazard ratios (including confidence intervals) in this situation are not valid because the hazards are non-proportional across the interval of follow up. The Committee noted the study authors concluded that the survival curves represented a delay in benefit with nivolumab. Members considered that the survival curves were suggestive of differential attrition of distinct populations in the study (where complications, adverse effects, differing biology, and early and late effects can all be possible causes of changes in a hazard rate over time).

*General comments*

- 3.22. The Committee considered that there was good quality and strength evidence for the use of nivolumab as monotherapy for the treatment of locally advanced or metastatic NSCLC that was directly relevant to a New Zealand setting.
- 3.23. The Committee considered that the currently available evidence supported an incremental gain in life expectancy with nivolumab over docetaxel for patients whose disease had progressed on or after platinum chemotherapy. The Committee considered that there was uncertainty regarding the level of benefit from nivolumab treatment in patients with squamous versus nonsquamous NSCLC.
- 3.24. The Committee noted that most patients enrolled in Checkmate017 and Checkmate057 had detectable rates of PD-L1 expression and were stratified by PDL1 status. The Committee considered that for squamous NSCLC PD-L1 expression was not proven to be predictive of prognosis or benefit. Members considered that for patients with nonsquamous NSCLC, higher PDL1 expression appeared to have the greatest incremental life expectancy gain from treatment with nivolumab. Members considered that PDL1 expression may be an appropriate biomarker to target treatment to those nonsquamous NSCLC patients that would benefit most but noted that further data was needed regarding this.
- 3.25. The Committee noted that the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia did not recommend that nivolumab be listed in the PBS for the treatment of squamous and nonsquamous NSCLC when this was considered in March 2016 on the basis that acceptable cost-effectiveness had not been adequately demonstrated. The Committee noted that pemetrexed was listed in Australia for the treatment of nonsquamous NSCLC but this agent was not currently funded in New Zealand.

3.26. The Committee considered that nivolumab as monotherapy should be funded for the treatment of locally advanced or metastatic squamous and nonsquamous NSCLC with a low priority, taking into account the high health need of the patient population but noting the immaturity of the data, the limited and uncertain incremental benefit over current treatments, and the high price sought by the supplier.

#### 4. Widening access criteria to Pulmonary Arterial Hypertension treatments

##### Application

4.1. The Committee considered an application from members of the PHARMAC Pulmonary Arterial Hypertension (PAH) Panel requesting widened access, including goal directed therapy, for PAH treatments on the Pharmaceutical Schedule. The two main requests were for:

- Patients with PAH in New York Heart Association (NYHA)/World Health Organization (WHO) Functional Classes III and IV (FC III/IV) to access earlier combination treatment; dual therapy without trialling two monotherapies, and escalating to triple therapy if the patient does not achieve 'low risk' status and;
- All patients in NYHA/WHO Functional Class II (FCII) with PAH to access treatment, including dual therapy,
  - without the requirement for clinical worsening (as is the case in the 2009 PHARMAC Eligibility Criteria for Pulmonary Arterial Hypertension Therapy) or;
  - having achieved FC II (ie improving from FC III and IV), for these patients to access dual therapy without trialling two monotherapies and escalating to triple therapy, if the patient does not achieve 'low risk' status – i.e. a 'goal directed' approach to treatment.

##### Recommendation

- 4.2. The Committee **recommended** that the application for the funding of Pulmonary Arterial Hypertension treatment for patients with PAH in NYHA/WHO Functional Classes III and IV for access to dual therapy following 3 to 6 months of sildenafil monotherapy be given a high priority.
- 4.3. The Committee **recommended** that the PAH Panel provide PTAC with an assessment about the evidence-based restriction criteria that might be used to determine the approach to dual therapy for patients who are unable to take sildenafil or other phosphodiesterase therapy.
- 4.4. The Committee **recommended** that the application for the funding of Pulmonary Arterial Hypertension treatments in all patients with PAH in NYHA/WHO Functional Class II be given a low priority.
- 4.5. The Committee deferred making a recommendation on the use of a goal-directed therapy approach and asked the PAH panel to provide PTAC with more direct evidence to support its use, and in particular assessment of cohort studies or randomised trials of this approach.
- 4.6. The Committee deferred making a recommendation for the application to fund triple therapy, pending additional evidence and asked the PAH panel to provide PTAC with direct evidence to support its use and in particular assessment of cohort studies or randomised trials of this approach.
- 4.7. The Committee has taken into account, where applicable, PHARMAC's current decision-making framework for these recommendations.

## **Discussion**

- 4.8. The Committee noted the currently funded PAH medicines and that the current mechanism for funding these medicines is via a treatment algorithm and eligibility criteria applied by the PAH Panel, determined in 2009. The Committee noted that under these criteria, patients with PAH in WHO (Venice) clinical classification groups 1, 4 and 5 who are in functional classes III and IV (FCIII/IV), and those in functional class II (FCII) patients with clear evidence of disease progression, have access to funded treatments. The Committee noted that currently funded agents include sildenafil, bosentan, ambrisentan, iloprost and epoprostenol, and that triple therapy is not funded.
- 4.9. The Committee noted that this application had been received requesting amendments to the 2009 eligibility criteria for PAH therapy. The Committee found the application was unclear and surmised that the application was requesting the following:
- Treatment be goal-directed in patients with PAH in FCII and FC III/IV
  - That the 2009 eligibility criteria for PAH therapy be widened to give all patients in FCII access to funded treatment, i.e. removing the 'clear evidence of progression' criterion
  - That the 2009 eligibility criteria for PAH therapy be changed to allow patients in all of FCII FCIII and FC IV, earlier access to dual therapy, and then to triple therapy, if they do not achieve a 'low-risk' status.
- 4.10. The Committee noted that the applicants had also submitted information regarding diagnostic testing with a fluid bolus which may help to determine differential diagnosis of PAH. However, the Committee noted that this was not directly related to the application for access to therapy and considered that it would more appropriate for the PAH Panel to advise PTAC and PHARMAC as to relevant diagnostic criteria.

### *Goal-directed therapy*

- 4.11. The Committee noted that goal-directed treatment was not well defined in the application. The Committee noted that the application was largely based on the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension (Eur Heart J doi:10.1093/eurheartj/ehv317), and from Figure 2 and Table 13, in this guideline, the Committee inferred goal-directed treatment to mean:
- Escalation from monotherapy to dual therapy if a patient remains FC III/IV after between three and six months of monotherapy, or if they have achieved FC II and they have any one of the 'intermediate' or 'high' risk assessment factors and that failure to achieve 'low' risk status, leads, to a recommendation for triple therapy (Figure 2).
  - Intermediate or high risk factors are summarised as: being in right heart failure, progression of symptoms, syncope, 6 minute walk distance (6MWD) <440m or cardiopulmonary exercise testing Peak VO<sub>2</sub> <15 ml/min/kg, BNP>50 ng/L, Right Atrial area >18 cm<sup>2</sup> or pericardial effusion, Right Atrial Pressure >8mmHg, cardiac index ≤2.5l/min/m<sup>2</sup>, and mixed venous oxygen saturation <65% (Table 13).
- 4.12. The Committee noted that there were a number of clinical measurements in Table 13 of the ESC/ERS Guidelines that were suggested as indicators of prognosis. The Committee considered that some of these measurements could only be assessed by invasive testing, and considered that it had not been provided with robust evidence that invasive testing would significantly alter the course of the disease by determining treatment escalation. The Committee considered that it had not been presented with robust evidence that

achieving all or a sub-set of these low-risk characteristics was associated with better quality of life or overall survival.

- 4.13. The Committee noted that the 6MWD is used to measure improvement in PAH. The Committee considered that the treatments for PAH were useful for symptomatic improvement, but there was less robust evidence that they were disease modifying. The Committee considered that a longer 6MWD was associated with better quality of life. The Committee considered however that an absolute value of 6MWD that is associated with an improved quality of life was difficult to determine from the evidence provided. The Committee considered that 6MWD is inherently variable because of patient factors including existing co-morbidities, energy levels, motivation, and some subjectivity (operator effort) and may have less validity and clinical relevance as an outcome measure particularly in studies where participants or evaluators were not masked as to treatment allocation.
- 4.14. The Committee noted that there was no direct evidence such as randomised controlled trials provided in the application with respect to ‘goal-directed’ therapy. The Committee noted that application had provided and discussed the European Cardiology Society (ECS)/European Respiratory Society (ERS) Guidelines, Table 13 (Eur Heart J doi:10.1093/eurheartj/ehv317). The Committee reviewed the references from these guidelines and considered that their recommendations were based on cohort studies, which they considered to be of moderate quality. The Committee considered that the available evidence did not indicate that ‘goal-directed’ therapy would lead to decreased mortality or morbidity, or improved quality of life in patients with PAH. The Committee considered that goal-directed therapy or any approach to treatment of PAH should be to improve quality of life and mortality rather than improving clinical parameters.
- 4.15. The Committee noted that the application may indirectly be requesting triple therapy, and considered that there was little evidence provided within the application to directly support this. The Committee noted that triple therapy is currently not funded under the current PAH treatment criteria. The Committee noted that according to the UK audit (National Audit of Pulmonary Hypertension 2015, Health & Social Care Information Centre) that up to 32% of patients with PAH may be candidates for triple therapy. The Committee considered that because the current PAH treatments are not disease modifying that they were uncertain about the clinical benefit that may be derived from the addition of a third therapy to dual therapy. The Committee deferred making a recommendation for the application to fund triple therapy, pending additional evidence and asked the PAH panel to provide PTAC with direct evidence to support its use and in particular assessment of cohort studies or randomised trials of this approach.

#### *PAH treatment for NYHA/WHO Functional Class II patients*

- 4.16. The Committee noted the evidence in the application for patients with PAH in NYHA/WHO FCII for access to treatment at diagnosis. Relevant trials for this proposal include the EARLY trial (Galie et al. Lancet 2008;371:2093), AMBITION trial (Galie N Engl J Med 2015;373:834-44), SERAPHIN trial (Pulido N Engl J Med 2013;369:809) and the COMPASS-2 trial (McLaughlin et al. Eur Respir J 2015;46(2):405-13).
- 4.17. The Committee noted the EARLY study (Galie et al. Lancet 2008;371:2093), a randomised controlled trial of 185 patients with PAH in FCII only, of placebo versus bosentan. The trial reported a mean 19 metre (95% CI -3.6 to 41.8) improvement in 6MWD after 6 month’s treatment, which the Committee considered was not significant clinically. The Committee considered that most patients in the study were on monotherapy with bosentan, which is not representative of the New Zealand population, where sildenafil is the first-line agent.
- 4.18. The Committee noted the AMBITION trial (Galie N Engl J Med 2015;373:834-44), a randomised controlled trial of ambrisentan and tadalafil versus ambrisentan or tadalafil, in 500 patients, 30% of whom were FCII. The Committee noted that 96% of patients were on

no treatment at the start of the trial. The study reported an improvement in functional class in 37% of patients on dual therapy and 33% of patients in the combined monotherapy group. The Committee noted that the hazard ratio for clinical worsening for dual therapy compared with the combined monotherapy trial arms for FCII was 0.21, versus the hazard ratio for FCIII which was 0.58. However, the Committee considered that the interaction by functional class for worsening was not statistically significant ( $p=0.08$ ), and hence considered that these results were consistent with the same relative clinical benefit of dual therapy for each level of baseline Functional Class, with the common HR of 0.50.

- 4.19. The Committee noted the SERAPHIN study (Pulido et al. *N Engl J Med* 2013;369:809), a randomised controlled trial of 500 patients adding macitentan versus adding placebo to usual care for PAH. The study population included patients with PAH who were 52% FCII and 47.5% FCIII or worse. In the treatment group the 6MWD difference was reported as 22 metres more, and there was an improvement in functional class in 13% of the placebo group and 22% of the treatment group. Members considered the supplement to the main paper for this study, which included a subgroup analysis for FCI/II versus III/IV for 6MWD. The supplement to the paper reported that for FCI/II the difference in 6MWD for macitentan versus placebo was 12 metres (95% CI -8.1 to 32.7), and for FCIII/IV this difference was 37m (95% CI 5.4 to 68.6). The Committee considered that this was consistent with FCI/II patients achieving less clinical benefit with the addition of macitentan, when compared with FCIII/IV.
- 4.20. The Committee noted the COMPASS-2 trial (McLaughlin et al. *Eur Respir J* 2015;46:405-13), a randomised controlled trial of bosentan added to sildenafil in 334 patients, where 42% of patients had FCII disease. The median duration of treatment was noted to be 23 months. The trial reported the overall hazard ratio was 0.88 (95% CI 0.6 to 1.29). The 6MWD was reported as 22m greater in the treatment group versus the placebo group (95% CI 5.9 to 37.8). An improvement in functional class was reported in 16% of patients. The Committee noted that approximately a third of patients withdrew from the study. The Committee noted that subgroup analysis by functional class reported no differences. The Committee considered that an improvement in 6MWD of 22m was unlikely to be clinically significant.
- 4.21. The Committee noted Lajoie et al. (*Lancet Respir Med* 2016;4:291-305), a systematic review and meta-analysis of 4095 participants in 17 studies of at least 12 weeks duration to assess the effects of monotherapy compared with combination therapies, with a main outcome of clinical worsening of PAH. The Committee noted that only 3 studies were of FCII patients, and that most studies had a follow up of less than 24 weeks. The Committee noted that the overall hazard ratio for clinical worsening for dual therapy versus monotherapy was 0.65 (0.58-0.72) and considered that for FCII versus FCIII/IV, the hazard ratios were similar (0.64 and 0.69 respectively) whilst the absolute risk reduction was less 10% in the FCII patients versus less 15% in the FCIII/IV patients. The Committee considered that the 6MWD was 20m greater in the group that received dual therapy. The Committee also noted that about 17% of patients in the dual therapy group had clinical worsening over a median duration of 16 weeks.
- 4.22. The Committee noted Badani et al. (*Heart, Lung and Circulation* 2016;25:46-52), a network meta-analysis of 4465 patients in 17 randomised controlled trials studying the effectiveness of treatments for PAH. The Committee noted that there were few trials that were longer than 24 weeks and that there was no statistically significant difference in the odds ratio for clinical worsening of PAH for any particular therapy versus placebo. The Committee considered that this systematic review did not indicate relevant clinical differences between the different classes of PAH therapy.
- 4.23. The Committee noted Kuwana et al. (*BMJ Open* 2013;3:e003113), a meta-analysis of 19 studies, including 9 studies of connective tissue disease PAH, a review of PAH treatment using 6MWD as the primary outcome. The Committee noted that there was an overall estimate in mean difference between changes in 6MWD of 34 metres, and questioned the

clinical significance of this. The Committee considered that a limitation of this meta-analysis was that no study was longer than 24 weeks.

- 4.24. The Committee noted Zhang et al. (Am Heart J 2015;170:96-103) a systematic review of oral therapies, which reported that after a mean follow up of five months, clinical worsening occurred in 18% of placebo and 11% of treatment patients. The odds ratio was reported as being 0.55 favouring treatment. Members considered that there was a moderate association between clinical worsening and baseline 6MWD.
- 4.25. The Committee considered that the available evidence, in relation to widening the 2009 Eligibility Criteria for PAH therapy to give all patients in FCII access to treatment, was of moderate quality and the strength of the evidence was moderate.

*Earlier combination PAH treatment for NYHA/WHO Functional Class III and IV patients*

- 4.26. The Committee noted the application for patients with PAH in NYHA/WHO Functional Classes III and IV to access earlier combination therapy, including the AMBITION trial (Galie et al. N Engl J Med 2015;373:834-44), SERAPHIN trial (Pulido et al. N Engl J Med 2013;369:809-18) and the COMPASS-2 trial (McLaughlin et al. Eur Respir J 2015;46(2):405-13). These trials are described in more detail, above.
- 4.27. The Committee noted the REVEAL longitudinal follow-up study of a US PAH registry, which included 2716 patients enrolled a median of 25 months after diagnosis with 38% patients in FCII and 54% of patients in FCIII. Benza et al. (Circulation 2010; 122:164-72) focussed on developing a prediction equation for survival, with proposed cut off values, including 6MWD <440m, BNP>50ng/L, and presence of pericardial effusion. The Committee considered that the development of these cut-off points was poorly described and may be inappropriate to predict survival rates. The Committee considered that the numbers of patients on monotherapy and dual therapy were poorly described in the paper.
- 4.28. The Committee noted Benza et al. (Chest 2012; 142:448-56), using data from the REVEAL cohort study with 2635 patients. The Committee noted that the survival rates were 85% at one year, 68% at 3 years, 57% at 5 years, and 49% at 7 years.
- 4.29. The Committee noted Barst (Chest 2013;144:160-8), which described a subgroup of 982 patients with PAH in FCIII at enrolment, in the REVEAL cohort study. The Committee noted that the authors did not describe the treatments that this cohort received. The Committee noted that 27% of patients had an improvement in functional class, 66% had no change in functional class, and 8% deteriorated. The 3 year survival in these groups was 84%, 64% and 29% respectively.
- 4.30. The Committee noted Nickel et. al (Eur Respir J. 2012;39:589-96), a longitudinal follow-up study of 123 patients with PAH from a German tertiary referral centre treated with goal-directed therapy (according to the protocol in Hoeper et al. Eur Respir J. 2005;26:585-63), for a median follow up of 38 months and 75% followed up for more than a year. For these patients, transplant free survival after one year was 92%, after two years it was 81%, and after 3 years 67%. The Committee noted that approximately half the patients died or had lung transplantation during follow up, and noted that the authors report that deterioration of functional class is a predictor for worse survival.
- 4.31. The Committee considered that the available evidence, in relation to patients with FCIII/IV PAH to access dual therapy after trialling one monotherapy, is of moderate strength and that the quality of the evidence is good.
- 4.32. The Committee considered Taichman et al. (Respir Res 2005;6:92-102), a cross sectional survey of 155 patients with new and previously diagnosed PAH at a tertiary referral centre in the US. The Committee noted that the predominant symptoms of patients in this study were dyspnoea, fatigue and weakness, light headedness and chest pain. The Committee

noted that 65% were married, 14% lived alone and 35% were currently employed. The Committee noted that the mean physical component score (PCS) in patients with PAH was 35, when normally in patients without PAH, the PCS is 50. For FCII, the PCS was 40, compared to PCS of 30 for FCIII patients.

- 4.33. The Committee considered Pepke-Zaba et al. (Chest 2008; 133:183-9), a 12 week study of 278 patients with PAH (40% in FCII, 60% in FCIII/IV) who were randomised to receive sildenafil or placebo, with a primary end point of 6MWD. In this study, health-related quality of life was recorded by patients using the short form 36 (SF-36) and EuroQol 5D (EQ-5D). The Committee noted that an increase in 6MWD of 45 metres was associated with an increase in the current health state and the utility index of the EQ-5D. The Committee considered that this may indicate that an increase in 6MWD may increase quality of life in patients with PAH.
- 4.34. The Committee noted that the applicant expected that 20% of all patients with PAH would be FC II. The Committee considered that this was an underestimate of the number of patients that would gain earlier access to PAH treatments under the proposal, given the distribution of FC classes entering clinical trials.
- 4.35. The Committee noted that the UK Audit (National Audit of Pulmonary Hypertension 2015, Health & Social Care Information Centre) indicated that survival at 2 years was similar for FCII and FCIII, at 80%. In FCII patients, monotherapy treatment failed 34% by two years, compared with 63% for FCIII, and 81% for FCIV. The Committee noted that only approximately 9% of patients in the audit were FCII. The Committee considered that this proportion was not representative of FC II patients in the New Zealand population, and considered that a ratio of 1:1 for FCII to FCIII patients, as reflected in clinical trials, would be more representative.
- 4.36. The Committee noted that PHARMAC staff estimated the number of patients with PAH in FC II based on the population prevalence of 50 patients per million (from Hoeper & Gibbs. Eur Respir Rev 2014;23: 450-7). The Committee considered that this underestimated the FCII population that would be eligible for treatment. The Committee considered that a ratio of 1:1 for FCII to FCIII patients, as reflected in clinical trials, would be more representative.
- 4.37. The Committee noted that no direct evidence regarding the health needs of, or treatment benefits to, the family was supplied in the application.

## 5. Selexipag for Pulmonary Arterial Hypertension

### Application

- 5.1. The Committee considered an application from Actelion Pharmaceuticals Australia Pty Limited for the funding of selexipag on the Pharmaceutical Schedule, as a monotherapy, dual therapy and a triple therapy, for patients with pulmonary arterial hypertension (PAH).

### Recommendation

- 5.2. The Committee **recommended** that funding of selexipag on the Pharmaceutical Schedule as monotherapy, dual therapy and triple therapy for PAH be given a low priority.
- 5.3. The Committee has taken into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

### Discussion

- 5.4. The Committee noted the proposal from Acetelion Pharmaceuticals Australia Pty Limited for the listing of selexipag as a treatment for PAH. The Committee noted that selexipag is a selective, non-prostanoid, IP (prostacyclin) receptor agonist. The Committee noted that selexipag is an oral tablet dosed at the maximum tolerated, titrated dose of 200mcg to 1600mcg twice daily.

- 5.5. The Committee noted the currently funded PAH medicines and noted that the current mechanism for funding these medicines is via a treatment algorithm and criteria applied by the PAH Panel. The Committee noted that under these criteria, patients with PAH in WHO classification groups 1, 4 and 5 who are in functional classes (FC) II (patients with clear evidence of disease progression), III and IV, currently have access to funded treatments. The Committee noted that dual therapy is only funded after two monotherapies have been trialled and not tolerated, and that triple therapy for PAH is not currently funded. The Committee noted that sildenafil, bosentan, ambrisentan and iloprost are available under the currently funded treatment algorithm.
- 5.6. The Committee noted that it has previously reviewed applications for PAH, including an application for macitentan which was reviewed at its May 2015 meeting and recommended to list with the same restrictions as bosentan with a low priority. The Committee also reviewed a proposal for widening of access for PAH treatments in FCII and FCIII/IV at this May 2016 PTAC meeting, recommending low priority and high priority respectively.
- 5.7. The Committee noted that PHARMAC staff estimate the prevalence of PAH to be similar to the UK estimate of 50 people per million. The Committee noted that PAH is an incurable, usually progressive condition. The Committee considered that surgery had a modest role, and in patients with severe PAH, considered that treatment was usually palliative whilst awaiting lung transplant. The Committee noted overseas series indicating 5 year survival of 60% for FC III patients and 30% for FC IV patients. The Committee noted that the health need of patients with PAH is variable, depending on their NYHA/WHO functional classification.
- 5.8. The Committee noted and reviewed the evidence supplied with this proposal, including the GRIPHON trial (Sitbon et al. NEJM 2015;37:3522-33) and the NS-304 trial (clinicaltrials.gov reference NCT00993408, ACT-293987).
- 5.9. The Committee noted the GRIPHON trial was a multicentre, randomised, double blind placebo-controlled, Phase 3 trial of 1156 patients with PAH, of 3 years duration with a composite end point of death or a complication related to PAH. A primary end point occurred in 397 patients (41.6% of placebo group, and 27% of selexipag group), hazard ratio (HR) 0.60; 99% confidence interval 0.46-078, P<0.001. The Committee noted that the primary end point comprised mostly of a reduction in hospitalisations and a decrease in disease progression. The Committee noted that death from any cause was 3.1% in the placebo group versus 4.9% in the selexipag group, which was reported as not statistically significant. The Committee noted that there was cross-over of 27% of patients from the placebo group to the selexipag group. The Committee noted that the trial did not indicate conclusive survival benefits of selexipag over placebo and noted that there was no significant difference in mortality reported between the two groups. The Committee noted that in the selexipag group the most common adverse effects were headache, diarrhoea, nausea, pain in jaw and worsening of PAH.
- 5.10. The Committee noted that in the GRIPHON trial, 32% of patients were on combination treatment (endothelin receptor antagonist and phosphodiesterase type 5 inhibitor) and there was a 37% risk reduction in this group, and considered that this group was most relevant to the New Zealand funded treatment setting. However, the Committee noted that the GRIPHON trial was for selexipag versus placebo (which was usual care, comprising PDE-5 +/- ERA), and considered that this was an appropriate comparator for New Zealand. The Committee noted that the GRIPHON trial included patients who were not receiving treatment for PAH and noted that the study population was group 1 PAH only.
- 5.11. The Committee considered that this was a well conducted, large randomised controlled trial. The Committee considered that the evidence in relation to selexipag was of high quality and the strength of the evidence was low.

- 5.12. The Committee considered that sildenafil and/or bosentan, or iloprost, may be suitable comparators to selexipag. Members considered that if PTAC was to give selexipag a positive recommendation, then selexipag may replace iloprost completely. The Committee noted that there are no head-to-head trials of selexipag versus iloprost.
- 5.13. The Committee noted that there were no trials of sildenafil versus selexipag, and considered that these would be necessary if there were to assess selexipag as a first line treatment.
- 5.14. The Committee noted that the available evidence did not include any studies regarding selexipag's impact on quality of life. The Committee considered that a study of selexipag and quality of life would assist in its evaluation of this pharmaceutical.
- 5.15. PTAC noted budget impact analysis undertaken done by PHARMAC staff and considered that the budget impact of this proposal, if selexipag was listed as a first line or second line agent in combination treatment, would be significant.

## **6. Dapagliflozin with metformin for type 2 diabetes mellitus**

### **Application**

- 6.1. The Committee considered an application from Astra Zeneca for the funding of dapagliflozin/metformin extended release combination tablet (Xigduo XR) for treatment of type 2 diabetes mellitus (T2DM).

### **Recommendation**

- 6.2. The Committee **recommended** that the application for funding of dapagliflozin/metformin extended release combination tablet, for the treatment of type 2 diabetes mellitus be declined.
- 6.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

### **Discussion**

- 6.4. The Committee noted that Xigduo XR is a combination tablet containing two oral anti-diabetic drugs: dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2), and metformin extended release, a biguanide.
- 6.5. The Committee noted that PHARMAC has received applications for the funding of three new classes of anti-diabetic agents and one combination antidiabetic medication since 2006, and noted that these applications had been reviewed by PTAC or the Diabetes Subcommittee.
- 6.6. The Committee noted that at its November 2013 meeting PTAC reviewed an application for dapagliflozin for the treatment of T2DM and recommended it be funded with a low priority. The Committee noted that at the August 2014 Diabetes Subcommittee of PTAC meeting, funding for all new anti-diabetic agents was recommended with a low priority, and that this recommendation has subsequently been ratified by PTAC.
- 6.7. The Committee noted that at the April 2015 Diabetes Subcommittee meeting, the Subcommittee reviewed the responses following a Request for Information (RFI), issued by PHARMAC, for the antidiabetic agents. The Committee noted that at this meeting the Diabetes Subcommittee, after considering responses from the RFI, recommended funding of at least one chemical from two of the three new classes of anti-diabetic agents, dipeptidyl peptidase 4 inhibitors (DPP4s), glucagon-like peptide-1 inhibitors (GLP-1s) or sodium glucose co-transporter 2 inhibitors (SGLT2s), and revised Special Authority criteria. The minutes of this meeting had subsequently been ratified by PTAC.

- 6.8. The Committee noted the proposed Special Authority criteria from the supplier and considered that there did not need to be further revision of the criteria, or that separate criteria should apply to this particular agent.
- 6.9. The Committee considered that, although there are recommendations for funding individual new antidiabetic agents with a low priority, there is a strong clinical desire to have access to at least one of the new diabetic agents.
- 6.10. The Committee considered the current treatment algorithms for T2DM (metformin, sulphonylureas, acarbose/pioglitazone, then insulin) and considered that pioglitazone and acarbose would be appropriate comparators to dapagliflozin. The Committee considered that patients may be treated with dapagliflozin to defer commencement of insulin. The Committee considered that in practice, patients with T2DM requiring a reduction in HbA1c of >0.5%, are likely to require initiation of insulin.
- 6.11. The Committee noted that metformin extended release as a single component was not registered with Medsafe, and that it had not previously considered it for funding. The Committee considered the mechanism of action of metformin, the side effects, and the cost and place in diabetes treatment. The Committee considered the clinical benefits of metformin were decreased weight and a reduction in HbA1c and that use of metformin was relatively contraindicated in renal impairment. The Committee considered that metformin extended release may have the advantage of decreased gastrointestinal side effects, which therefore could increase tolerability; although noted that it has not previously considered metformin extended release as a single agent. With regards to efficacy, the Committee considered that it appeared to be similar to immediate release metformin.
- 6.12. The Committee noted that there was a low risk of hypoglycaemia on dapagliflozin, but that there was no indication of how frequently blood glucose levels should be tested. The Committee considered testing blood glucose would still be required as patients will need to ensure that their glycaemic control is adequate.
- 6.13. The Committee considered Sun et al (BMJ Open 2014;4:e004619), a meta-analysis evaluating the synergistic efficacy of dapagliflozin versus placebo in combination with conventional antidiabetic medications, to determine changes in glycosylated haemoglobin and weight on dapagliflozin. The authors reported that, for metformin and dapagliflozin versus metformin alone, the reduction in HbA1c was -0.47% (95% CI -0.6 to -0.34), and that the overall effect size of HbA1c calculated from mean difference was -0.52% (95% CI -0.6 to -0.45). The Committee noted the effect size on body weight was -2.1 kg (95% CI -2.32 to -1.88kg), and in patients who were treated with dapagliflozin and metformin, the effect size was -2.17kg (95%CI -2.52 to -1.81kg). The Committee considered that weight may not be a good surrogate marker for body mass index, and may not significantly alter clinical outcomes. The Committee considered that there did not appear to be any clinically significant synergistic effects from taking the two drugs (metformin and dapagliflozin) as a combination product compared to the two drugs as individual components.
- 6.14. The Committee considered Plosker et al (Drugs 2014; 74:2191-2209), a review of dapagliflozin in patients who have T2DM, focussing on long-term efficacy and trial data. The Committee noted that after 102 weeks when dapagliflozin was given with metformin, the placebo-corrected change in HbA1c from baseline was -0.6% with dapagliflozin 5mg per day and -0.7% with dapagliflozin 10mg per day. The Committee noted that the most common adverse effects in the group taking dapagliflozin were female genital mycotic infections (8.4% in those taking 10mg/day dapagliflozin, 6.4% in those taking 5mg/day dapagliflozin, 1.5% in the placebo group) and urinary tract infections (9.5%, 7.7% and 6.6% respectively). The Committee noted that patients with type 2 diabetes are at a higher risk of fungal and genital infections and UTIs compared with the general population, and expressed concerns with regards to this particular adverse event. The Committee noted that this review reports that dapagliflozin is associated with small mean

changes in fasting serum lipid parameters compared with placebo at 24 weeks. The pooled analysis of 12 studies indicated that in the dapagliflozin groups, there was an increase from baseline in LDL cholesterol of 0.6-2.7% and an increase in total cholesterol from 1.1-1.4%. In placebo patients, there was a reduction of LDL of 1.9% and 0.4%. The HDL cholesterol levels were increased in the dapagliflozin 5mg, 10mg and placebo groups by 6.5, 5.5 and 3.8% respectively. The Committee considered the long term significance of the reported changes in lipids was unclear.

- 6.15. The Committee considered Zinman et al (N Engl J Med 2015; 373:2117-28), a randomised double blind, placebo controlled trial of empagliflozin in 7020 patients at 590 sites in 42 countries to assess the cardiovascular morbidity and mortality in patients with T2DM and high cardiovascular risk. The primary composite outcome, which comprised of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, occurred in 10.5% of the pooled empagliflozin group and 12.1% of the placebo group (Hazard Ratio 0.86, 95% CI 0.74-0.99). The secondary composite outcome was the primary outcome plus hospitalisation for unstable angina, and the study reported no significant between-group differences in the secondary outcome. Post-hoc analysis of the study data reported that patients who received empagliflozin had a lower rate of death from cardiovascular cause, death from any cause and hospitalisation for heart failure. The Committee considered that it was unclear how the results from this study correlated to clinical care.
- 6.16. The Committee considered Odegard and Capoccia (The Diabetes Educator 2007; 33: 1014-29), a systematic review of literature evaluating medication adherence and diabetes mellitus. The Committee considered that increases in dosing frequency may be a barrier to adherence; however, noted that there are several barriers to adherence. The Committee considered that no evidence had been provided to demonstrate that a fixed dose combination tablet would significantly increase adherence and clinical outcomes. The Committee considered that patients with T2DM are often on a large number of medications and combining two of these medications into a fixed dose combination pill, is not likely to make adherence to the remaining medications easier.
- 6.17. The Committee considered a limitation of the evidence included in this application to be that there were no New Zealand or Australian participants in the studies.
- 6.18. The Committee noted that it is estimated that there are over 200,000 people diagnosed with diabetes in NZ and that rates of diagnosed diabetes are higher in Maori, Pacific and Asian New Zealanders than in European/Other ethnic groups. The Committee considered that people with T2DM have a high health need, due to the long term microvascular and macrovascular complications associated with the disease. The Committee considered the health needs of family members/carers and that they may experience anxiety with regards to the management of a person with diabetes. The Committee considered that a reduction in microvascular/macrosvascular complications would provide additional benefits to the health need of family, whanau or wider society; however, there was no available evidence to suggest that dapagliflozin/metformin ER would provide this.
- 6.19. The Committee considered that the fixed dose combination was more expensive than the individual components and that superiority of the fixed dose combination over the individual components had not been demonstrated. The Committee expressed concerns with recommending funding for a combination, when the individual components were not funded. The Committee noted that, although the adverse events in the trials were reported to be generally mild to moderate, prescribers did not have experience with the individual components alone and that the combination may not be appropriate for use in patients with multiple comorbidities and the elderly population.
- 6.20. The Committee considered that funding of dapagliflozin/metformin ER would result in a high budget impact and have a high cost per quality-adjusted life year.

## **7. Taurolidine and citrate solution**

### **Application**

- 7.1. The Committee considered a clinician funding application from the Nutrition Support Team at Auckland District Health Board (ADHB) for the new listing of taurolidine and citrate catheter lock solution (Taurolock) in the Pharmaceutical Schedule. The Committee also considered supplementary information provided by the supplier Rollex Medical.

### **Recommendation**

- 7.2. The Committee **recommended** that taurolidine and citrate catheter lock solution (Taurolock) be listed in Section H of the Pharmaceutical Schedule for the locking of central venous access devices in those at high risk of developing central line-associated bacteraemia (CLAB) or patients with limited vascular access options due to previous line-related complications, only if cost-neutral to ethanol 70% catheter lock solution.
- 7.3. The Committee **recommended** that Taurolock be considered by the Anti-Infective Subcommittee of PTAC at its next meeting.
- 7.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### **Discussion**

- 7.5. The Committee noted Taurolock is a catheter lock solution containing (cyclo)-taurolidine (1%) and citrate (4%), with anticoagulant and antimicrobial properties, which is registered as a device with Medsafe.
- 7.6. Taurolock is instilled in the lumen of central venous access devices (CVADs) between treatments in order to prevent microbial colonisation and reduce the likelihood thrombus formation which may cause catheter occlusion. The Committee noted Taurolock is marketed as preventing both infection and occlusion in ports and silicone/polyurethane catheters used in oncology, haemodialysis, intensive care and parenteral nutrition. The Committee noted the solution must be withdrawn prior to initiating the next treatment.
- 7.7. The Committee noted central line-associated bacteraemia (CLAB) is associated with increased mortality and morbidity, as well as significant costs to the healthcare system. The Committee considered prevention of CLAB was likely to be the primary benefit associated with Taurolock. The Committee considered that ethanol 70% catheter lock solution is therefore most appropriate comparator for Taurolock.
- 7.8. The Committee noted that the choice of catheter locking solution may have a role in reducing CLAB in high-risk patients by reducing the bacterial biofilm that forms on catheter surfaces. The Committee noted there is good evidence that standardised insertion, maintenance and removal practices are effective at reducing the incidence of CLAB, and are the subject of an ongoing project led by the Health Quality and Safety Commission (HQSC).
- 7.9. The Committee noted heparin catheter locks are commonly used to prevent catheter occlusion in adult and paediatric patients who are having their CVAD accessed frequently and in those patients who are at lower risk of developing CLAB. The Committee noted that one of the complications of catheter related thrombosis is CLAB (Baskin et al, Lancet 2009;374:159-69).
- 7.10. The Committee noted that patients at high risk of developing CLAB could include those who have previously developed CLAB or those who are indicated for but not tolerated ethanol 70% catheter lock solution. The Committee noted higher cost of Taurolock and ethanol 70% catheter lock solutions compared to sodium chloride and heparin locks, and considered there was a fiscal risk if there was substitution from these less expensive locking solutions. The Committee therefore considered Taurolock appropriate to list if

cost-neutral to ethanol 70% catheter lock solution for those patients who would otherwise have been prescribed ethanol 70% catheter lock solutions.

- 7.11. The Committee considered it would be difficult to restrict the use of Taurollock to situations of secondary prevention of CLAB. The Committee noted there may be a fiscal risk with listing, as Taurolock may replace some use of heparin or sodium chloride locking solutions.
- 7.12. The Committee noted the applicant expressed concern that the use of ethanol 70% catheter locks may compromise the integrity of intravenous catheters over time, can be associated with systemic effects, and that it may be ineffective at preventing the growth of biofilms on the catheter lumen surface, however evidence to support that concern was not provided.
- 7.13. The Committee noted a systematic review by Mermel and Alang (J Antimicrob Chemother. 2014;69:2611-9) including a number of small non-blinded predominantly retrospective trials reporting the adverse effects associated with ethanol catheter lock solutions. Adverse events noted in these trials included evidence of catheter degradation or malfunction, systemic ethanol exposure and catheter occlusion. The Committee noted the in vitro evidence of deterioration after ethanol immersion, which was predominantly observed in polyurethane catheters and to a lesser extent, silicone and carbothane catheters. The Committee considered there is insufficient evidence of clinical consequences associated with the use of ethanol 70% locking solutions and supported the author's conclusion that large, prospective, randomized trials are needed.
- 7.14. The Committee considered there is a lack of direct comparison studies between the use of ethanol lock solutions and Taurollock in preventing CBRSI or catheter occlusion. The Committee noted a case-study by Chan (Poster Abstract, 40th SHPA Conference. 2014) observing one patient with home parenteral nutrition (HPN) transition from 70% ethanol lock to Taurollock due to supplier stock issues. There was no report of CLAB from patient being on either catheter lock solutions.
- 7.15. The Committee noted a systematic review and meta-analysis by Liu et al (PLoS One. 2013;8:e79417) of randomised trials comparing the use of taurolidine to heparin lock solutions in the prevention of CLAB. The Committee considered heparin was a poor comparator if the outcome of interest is preventing CLAB. Six randomised-control trials involving 431 patients and 86,078 catheter-days were included in the review. The results showed a significantly lower incidence of CLAB with taurolidine compared to heparin lock solutions (Risk Ratio [RR], 0.34; 95% Confidence Interval [CI], 0.21–0.55). In particular, taurolidine showed reduced incidence of CLAB from gram-negative bacteria ( $P = 0.004$ ; RR, 0.27; CI, 0.11–0.65), but a non-significant reduction from gram-positive bacteria ( $P = 0.07$ ; RR, 0.41; CI, 0.15–1.09) due to limited data. No significant association was observed with taurolidine and catheter-related thrombosis (RR, 1.99; CI, 0.75–5.28). Members considered both the meta-analysis and the included studies were generally of a low quality with a number of methodological and technical deficiencies
- 7.16. The Committee noted that the trial by Solomon et al (Am J Kidney Dis. 2010;55:1060-8), which contributed a significant number of patients in the Liu et al meta-analysis, found there was a greater need for thrombolytic therapy in the taurolidine and citrate lock solution group versus heparin (hazard ratio, 2.5; 95% CI, 1.3-5.2;  $P = 0.008$ ). According to Liu et al, this trial by Solomon et al was the only rigorously conducted randomised controlled trial.
- 7.17. The Committee noted an open-label prospective study by Bisseling et al (Clin Nutr. 2010;29:464-8) comparing taurolidine to heparin in preventing CLAB for patients on home parenteral nutrition (HPN). Thirty patients identified as high-risk after developing catheter related blood stream infection were randomised to continue HPN using heparin (n=14) or taurolidine (n=16) catheter lock solutions. The study results reported 10 re-infections in heparin group and one re-infection in the taurolidine group during 5370 catheter days.

The mean infection-free survival was 175 days (95% confidence interval (CI), 85-266; heparin) versus 641 days (95% CI 556-727; taurolidine); log-rank p < 0.0001. Further cross-over from the 10 patients with re-infections from the heparin group to taurolidine reported only one new infection. The Committee noted there were no adverse reactions or catheter occlusions in either group. The Committee noted this trial had a number of limitations reducing its applicability including the control group being heparin, a small sample size, lack of blinding, the diagnosis not based on tip culture and 12 patients went into study with old catheter but it is not clear which group they were allocated to.

- 7.18. The Committee noted a retrospective study by Saunders et al (Eur J Clin Nutr. 2015;69:282-4) comparing taurolidine to heparin in preventing CLAB in twenty-two patients on home parenteral nutrition (HPN). The overall CLAB rate pre- and post-taurolidine use was reduced from 5.71 to 0.99 infections per 1,000 patient parenteral nutrition days (P < 0.0001). In patients with two or more episodes of CLAB acquired in the community in a period of <12 months (n=13) the incidence of CLAB reduced from 36 to 10 per 1,000 patient parenteral nutrition days.
- 7.19. The Committee noted a study Chu et al (J Pediatr Gastroenterol Nutr. 2012;55:403-7) compared the use of Taurolock and heparin in preventing CLAB in children on HPN. Nineteen children were identified with previous infection while on heparin locks. There were 8.6 episodes of CLAB per 1,000 catheter days with heparin and 1.1 episodes per 1,000 catheter days with Taurolock (P=0.002). A total of 14 out of 19 children (74%) had no infections for up to 33 months after changing to Taurolock. The Committee considered this had limited applicability given the small patient number, the lack of a control group and the high risk of bias.
- 7.20. The Committee noted a randomised prospective trial by Betjes and van Agteren (Nephrol Dial Transplant. 2004;19:1546-51) comparing the use of Taurolock to heparin as catheter lock solutions in CLAB prevention in dialysis. A total of 58 patients and 76 catheters inserted were included in this study. Blood cultures were taken every 2 weeks until either culture became positive for bacteria or until time of catheter removal. The reported incidence of catheter colonisation progressed slowly with no difference between Taurolock to heparin catheter lock solutions. The number of exit-site infections was also similar between both groups.

## 8. Cinacalcet for patients with parathyroid disorders

### Application

- 8.1. The Committee considered the funding of cinacalcet on the Pharmaceutical Schedule for patients with parathyroid disorders.

### Recommendation

- 8.2. The Committee **recommended** the following changes to the current Special Authority for cinacalcet for parathyroid carcinoma (additions in bold, deletions in strikethrough):

#### Special Authority for Subsidy

**Initial application** only from a nephrologist or endocrinologist. Approvals valid for 6 months for applications meeting the following criteria:

Either:

- 1 All of the following:
  - 1.1 The patient has been diagnosed with a parathyroid carcinoma (see Note); and
  - 1.2 The patient has persistent hypercalcaemia (serum calcium  $\geq 3$  mmol/L) despite previous first-line treatments including **sodium thiosulfate (where appropriate)** and bisphosphonates and ~~sodium thiosulfate~~; and
  - 1.3 The patient is symptomatic; or
- 2 All of the following:
  - 2.1 The patient has been diagnosed with calciphylaxis (calcific uraemic arteriolopathy); and

- 2.2 The patient has symptomatic (e.g. painful skin ulcers) hypercalcaemia (serum calcium  $\geq 3$  mmol/L); and
- 2.3 The patient's condition has not responded to previous first-line treatments including bisphosphonates and sodium thiosulfate.

**Renewal** only from a nephrologist or endocrinologist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Both:

- 1 The patient's serum calcium level has fallen to  $< 3$  mmol/L; and
- 2 The patient has experienced clinically significant symptom improvement.

Note: this does not include parathyroid adenomas unless these have become malignant.

- 8.3. The Committee **recommended** that funding of cinacalcet on the Pharmaceutical Schedule for patients with non-malignant primary hyperparathyroidism with symptomatic hypercalcaemia contraindicated to surgery, or where previous surgery has been unsuccessful, be declined.
- 8.4. The Committee **recommended** that the funding of cinacalcet in patients with tertiary hyperparathyroidism with symptomatic hypercalcaemia, including those patients contraindicated to surgery or where previous surgery has been unsuccessful, be declined.
- 8.5. The Committee **recommended** that the funding of cinacalcet in patients with non-malignant secondary hyperparathyroidism with symptomatic hypercalcaemia, including those patients contraindicated to surgery or where previous surgery has been unsuccessful, and regardless of whether or not the patient is on dialysis, be declined.
- 8.6. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

## Discussion

- 8.7. The Committee noted that it had previously reviewed the funding of cinacalcet for treatment of elevated calcium levels in patients with parathyroid disorders, most recently in November 2015.
- 8.8. The Committee noted that at its November 2015 meeting it had recommended that cinacalcet funding be declined for: non-malignant parathyroid disorders (any cause) without symptomatic hypercalcaemia; non-malignant secondary hyperparathyroidism with or without elevated serum calcium, except in the limited setting of calciphylaxis after other treatments have been tried and failed; tertiary hyperparathyroidism and elevated serum calcium; primary hyperparathyroidism and elevated serum calcium without an absolute contraindication for parathyroid surgery.
- 8.9. The Committee noted that it had recommended that cinacalcet be funded on the Pharmaceutical Schedule in hospitals and community for patients with parathyroid carcinoma with symptomatic hypercalcaemia unresponsive to other treatments, and for patients with symptomatic calciphylaxis only after failure of bisphosphonates and sodium thiosulfate, subject to Special Authority criteria/hospital restrictions with a medium priority. The Committee noted that PHARMAC had made a decision to fund cinacalcet for these indications from 1 May 2016.
- 8.10. The Committee noted that PHARMAC staff were seeking updated advice from the Committee on the funding of cinacalcet for various indications following receipt of submissions from two suppliers (Amgen in relation to the Sensipar brand and Te Arai BioFarma in relation to a generic brand) as well as responses to consultation on the above funding decision requesting wider funded access to cinacalcet and other feedback received from Named Patient Pharmaceutical Assessment (NPPA) applicants.

### *Parathyroid carcinoma*

- 8.11. The Committee noted that a NPPA applicant had queried the evidence for requiring a trial of sodium thiosulfate prior to cinacalcet in settings other than calciphylaxis. The Committee noted that sodium thiosulfate was listed only in Section H of the Pharmaceutical Schedule and that only one strength (250 mg/ml) is currently registered in New Zealand.
- 8.12. The Committee considered that evidence for sodium thiosulfate in settings other than calciphylaxis was lacking and, on this basis, it would be reasonable to remove sodium thiosulfate as a pre-requisite for the funded indication of parathyroid carcinoma. However, the Committee noted that it was possible that a patient with parathyroid carcinoma could have calciphylaxis as their primary symptom, in which case it would be reasonable for sodium thiosulfate to be trialled. Therefore, the Committee considered that it would be reasonable to amend the wording on the Special Authority to make it clear that sodium thiosulfate should be trialled in patients with parathyroid carcinoma “where appropriate.”

### *Primary hyperparathyroidism including patients contraindicated to surgery or where previous surgery has failed*

- 8.13. The Committee noted a publication provided in a submission from Te Arai BioFarma. This was a 4.5 year open-label extension study of 45 patients with mild to moderate primary hyperparathyroidism from a double-blind, placebo-controlled, one-year trial (Peacock et al. J Clin Endocrinol Metab 2005;90:135-41). Compared with baseline, cinacalcet treatment reduced serum calcium and parathyroid hormone (PTH), increased serum phosphate, and slightly increased alkaline phosphatase. There were no significant effects on bone mineral density, which the authors attributed to a number of possible mechanisms, including the fact that the majority of subjects had mild disease and normal bone turnover markers at baseline.
- 8.14. The Committee noted its previous comments regarding the limited evidence for cinacalcet in patients with primary hyperparathyroidism. The Committee considered that this remained the case, noting that no new evidence for long-term clinically meaningful benefits of cinacalcet in this patient group had been presented since it last reviewed the evidence in November 2015. The Committee considered that this lack of evidence applied regardless of the patient’s ability to undergo surgery, whether or not prior surgery had been unsuccessful, and whether or not the patient had symptomatic or asymptomatic hypercalcaemia.

### *Tertiary hyperparathyroidism*

- 8.15. The Committee noted its previous comments that tertiary hyperparathyroidism occurs in patients with long-standing secondary hyperparathyroidism, almost always in the setting of chronic renal failure, and reflects development of autonomous (unregulated) parathyroid function following a period of persistent parathyroid stimulation.
- 8.16. The Committee noted that at its November 2015 meeting it had recommended that cinacalcet funding be declined for tertiary hyperparathyroidism and elevated serum calcium.
- 8.17. The Committee noted that, during recent consultation on a proposal to fund cinacalcet for calciphylaxis and parathyroid carcinoma, PHARMAC had received multiple requests to include funding of cinacalcet for severe/refractory tertiary hyperparathyroidism, particularly where parathyroidectomy is contraindicated or had been unsuccessful.
- 8.18. The Committee noted that at least one consultation responder had included supporting evidence; however, the publications provided appeared to be primarily relating to the use of cinacalcet in patients with secondary hyperparathyroidism (discussed below).

8.19. The Committee noted that in the real world setting there appeared to be some ambiguity about the diagnosis of secondary versus tertiary hyperparathyroidism. However, given that no new evidence had been provided for the use of cinacalcet in tertiary hyperparathyroidism (as defined above), the Committee reiterated its previous view that cinacalcet should not be funded for this indication, regardless of whether or not surgery was contraindicated or had been unsuccessful.

#### *Secondary hyperparathyroidism*

8.20. The Committee noted two submissions from suppliers in support of the funding of cinacalcet for patients with secondary hyperparathyroidism:

- A submission from Amgen requesting funding of cinacalcet (Sensipar) for patients with secondary hyperparathyroidism who are on dialysis, with PTH levels greater than nine times the upper limit of normal (ULN), alkaline phosphatase greater than the ULN and who are medically unsuitable for parathyroidectomy or previous parathyroidectomy has failed.
- A submission from Te Arai BioFarma requesting funding of cinacalcet (generic brand) for patients with secondary hyperparathyroidism on renal haemodialysis with symptomatic hypercalcaemia.

8.21. In addition, the Committee noted evidence for the use of cinacalcet in patients with secondary hyperparathyroidism that was included in a consultation response (as noted above).

8.22. The Committee noted that patients with secondary hyperparathyroidism on dialysis have a high health need. The Committee noted that potential available treatment options included vitamin D analogues, bisphosphonates and phosphate binders. The Committee noted that the only non-calcium phosphate binder available in New Zealand is aluminium hydroxide, which is associated with concerns about aluminium toxicity.

8.23. The Committee noted that it had previously discussed the use of cinacalcet in the secondary hyperparathyroidism setting and had concluded that, while there was good evidence supporting the efficacy of cinacalcet in reducing biochemical markers such as serum calcium and PTH, the evidence for a beneficial effect on clinically meaningful outcomes such as fracture risk and mortality risk was poor or lacking.

8.24. The Committee reviewed all the publications provided and, in particular, noted the clinical and quality of life findings described in some of the publications, summarised briefly below:

- Akizawa et al. PTH-dependence of the effectiveness of cinacalcet in hemodialysis patients with secondary hyperparathyroidism. *Sci Rep* 2016;6:19612. This was a prospective case-cohort and cohort study involving 8229 patients with CKD stage 5D requiring maintenance haemodialysis who had secondary hyperparathyroidism. The authors reported that in patients with PTH  $\geq 500$  pg/ml, the reduction in the risk of death from any cause was about 50% (Incidence Rate Ratio [IRR] = 0.49; 95% Confidence Interval [95% CI]: 0.29–0.82); for a composite of cardiovascular hospitalisation and mortality, the association was not statistically significant. The Committee noted that this was a non-experimental and highly complex study design with issues in methodology (e.g. potential for type I error rate inflation) and, as such, the findings should be treated with caution. The Committee considered that a statistically significant finding in a single subgroup, in the absence of a highly plausible biological mechanism, was hypothesis generating but not clinically relevant.
- Parfrey et al. Lessons Learned from EVOLVE for Planning of Future Randomized Trials in Patients on Dialysis. *Clin J Am Soc Nephrol*. 2016;11:539-46. This paper discusses a number of reasons why the EVOLVE trial did not produce a positive

outcome. The authors note that the chance imbalance in mean age at baseline between the two groups may have affected the outcome. Using a post-hoc (not pre-specified) multivariable-adjustment to account for this, the ITT relative hazard for the primary outcome was 0.88, which was statistically significant (95% CI, 0.80 to 0.98). The Committee considered that this statistical modification did not provide compelling evidence of efficacy of cinacalcet in reducing the risk of the primary outcome (composite of all-cause mortality or non-fatal CV events).

- Parfrey et al. The Effects of Cinacalcet in Older and Younger Patients on Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. *Clin J Am Soc Nephrol.* 2015;10:791-9. This was a post-hoc subanalysis of the EVOLVE trial by age group. The authors reported that cinacalcet reduced the risk of death and major cardiovascular events in older, but not younger, patients with moderate to severe secondary hyperparathyroidism who were receiving haemodialysis. The authors provide several possible reasons for this finding. The Committee considered that the large number of endpoints considered in this subgroup analysis resulted in a high risk of bias and noted that the substantial issues with the EVOLVE study (for example, compliance, definition of end points, differential application of interventions) were not addressed by this.
- Chertow et al. Self-reported symptoms in patients on hemodialysis with moderate to severe secondary hyperparathyroidism receiving combined therapy with cinacalcet and low-dose vitamin D sterols. *Hemodial Int.* 2012;16:188-97. This was a multicentre open-label industry funded study (TARGET) with 569 subjects enrolled in two cohorts – moderate to severe and advanced. The study design included a dose titration phase for 8 or 14 weeks respectively, an efficacy phase for 8 weeks for both groups then followed for 52 weeks or until study was terminated upon FDA approval of cinacalcet. Outcome measures included a 14 symptom questionnaire derived from the Kidney Disease QOL survey (KDQOL) and SF-36. Baseline QoL scores were fairly similar between two cohorts with the exception of some pain scores. With the exception of one item, the score for frequency of all symptoms accessed by the Kidney QoL questions improved numerically from baseline to end of efficacy phase. For 8 of the 14 symptoms the improvement was statistically significant. Improvements were generally maintained until the end of study. The Committee considered that the clinical significance of the small symptom score changes was unclear, noting that it was unclear if the outcome measure had been validated and what the minimally clinically important change would be. The Committee noted that there were no clinically or statistically significant changes in any of the SF-36 subscales or in any of the physical or mental health composite scores.
- Messa et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol.* 2008;3:36-45. This was a multicentre, open label study in patients with poorly controlled secondary hyperparathyroidism randomised to receive conventional care (n = 184) or cinacalcet (n=386). The study design included a 16 week optimisation phase and 7 week efficacy phase; the primary end point was the proportion of patients with PHT <300 pg/ml. Patient reported outcomes were assessed at screening and end of each study phase (weeks 15 and 23) using EQ-5D and KD QOL-SF. The mean (SD) QOL scores at baseline were similar in both groups and remained essentially unchanged in each group throughout the study.

- 8.25. The Committee also noted recent systematic reviews and meta-analyses of trials in patients with chronic kidney disease comparing cinacalcet with standard treatment (Sekercioglu et al. *Ren Fail.* 2016 May 2:1-18 [Epub ahead of print]; Ballinger et al. *Cochrane Database Syst Rev* 2014;12:CD006254). The authors reported that the results left considerable uncertainty regarding the impact of cinacalcet on reducing fractures, and indicated that cinacalcet did not reduce hospitalisations due to cardiovascular events and did not reduce cardiovascular mortality or all-cause mortality, but reduced the need for

parathyroidectomy (absolute effect 55 fewer per 1000). Cinacalcet increases the risks of nausea, vomiting and hyopcalcaemia.

- 8.26. Taking into account previous Committee reviews and Subcommittee advice, the Committee considered that the available body of evidence continued to support the efficacy of cinacalcet in reducing PTH and serum calcium in secondary hyperparathyroidism. However, the Committee reiterated its previous view that good quality evidence for cinacalcet in improving clinically important outcomes was generally lacking. Therefore, the Committee considered that cinacalcet should not be funded for this indication.

#### *General remarks*

- 8.27. The Committee noted that several submissions to PHARMAC, including consultation responders, considered that the use of cinacalcet would reduce the need for parathyroidectomy. The Committee considered that the number of avoided parathyroidectomies from the use of cinacalcet in New Zealand was likely to be very small. Further, the Committee considered that the available evidence favoured parathyroidectomy over cinacalcet in terms of efficacy outcomes (eg Cruzado et al. J Am Soc Nephrol. 2015;pii: ASN.2015060622 [Epub ahead of print]).
- 8.28. The Committee noted that NPPA applicants frequently provided evidence of reductions in PTH levels in support of renewal applications for cinacalcet. The Committee noted that PHARMAC staff requested guidance as to whether or not this measure was a relevant efficacy measure. The Committee considered that it was not a relevant efficacy measure, as cinacalcet is expected to reduce PTH levels in all patients, given its mechanism of action. The Committee reiterated its previous view that renewal applications should provide evidence of normalisation of calcium levels (to below 3 mmol/l) and clinically significant symptom reduction.

## **9. Micronutrients for people with ADHD and/or mood dysregulation**

### **Application**

- 9.1. The Committee considered an application for the funding of micronutrients (Hardy Nutritionals Daily Essential Nutrients and/or EMPowerPlus Advanced) for the treatment of attention deficit and hyperactivity disorder (ADHD).

### **Recommendation**

- 9.2. The Committee **recommended** that the application for the funding of micronutrients (Hardy Nutritionals Daily Essential Nutrients and/or EMPowerPlus Advanced) for the treatment of attention deficit and hyperactivity disorder (ADHD) be declined.
- 9.3. The Committee has taken into account, where applicable, PHARMAC's current decision-making framework as appropriate in relation to its advice for this recommendation.

### **Discussion**

- 9.4. The Committee noted that ADHD is a disorder with a range of symptom domains and severity ranging from mild to very severe. The Committee noted that ADHD affects children and adults differently: in children the key impacts include impaired learning and detrimental impacts on relationships and attachment, whereas in adults the key impacts include decreased ability to perform normal functions (e.g. retaining employment) and detrimental impacts on relationship and child-rearing.
- 9.5. The Committee noted the range of prevalence figures for ADHD is very variable internationally (Polanczyk et al. Am J Psychiatry 2007;164:942-8). The Committee considered that, based on the available information, for the purposes of PHARMAC's

analyses it would be reasonable to estimate the prevalence of ADHD in children at 5.5% and adults at 4.4%.

- 9.6. The Committee considered that individuals with untreated ADHD experience significant difficulties in their ability to conduct usual activities, noting that the diagnosis of ADHD requires impairment in two or more domains, is often associated with co-morbidities, impacts key functional capacity and is associated with poorer physical and mental health outcomes.
- 9.7. The Committee noted that ADHD is more common in people with low socioeconomic status. The Committee noted that it was not aware of any evidence to suggest that ADHD was more prevalent in Māori and Pacific peoples, independent of socioeconomic status. The Committee noted that evidence suggests that there is a genetic component to ADHD, which can lead to intergenerational ADHD.
- 9.8. The Committee noted that ADHD can carry a significant burden for whānau, although the degree and severity of this burden is not well described in the literature. The Committee noted that the impacts of ADHD in children can impact on peer relationships, interactions in the home and learning. The Committee noted that impacts of ADHD in adults can lead to increased violence, aggression, intimate relationship problems and increased family stressors (Newton-Howes G. J R Soc Med 2004;97:531-5).
- 9.9. The Committee noted that effective treatment of ADHD can have positive effects on the patient and family, whānau and wider society, through improvements in social attention and reduction in attachment/emotional problems in children and adults and criminality in adults.
- 9.10. The Committee noted that currently funded treatments for people with ADHD include atomoxetine, dexamfetamine and various formulations of methylphenidate (immediate-release, sustained-release, extended/modified-release), all of which are subject to Special Authority restrictions for funding. The Committee considered that there were no significant problems with access to currently funded treatments, although two of the treatments (dexamfetamine and methylphenidate) had legal requirements for prescriptions to be written by a paediatrician or psychiatrist or on the recommendation of one of these specialists.
- 9.11. The Committee noted that the funded treatments had been extensively researched although recent meta-analyses suggested that the benefits may not be as great as previously thought (eg Storebø et al. Cochrane Database Syst Rev 2015 Nov 25;11:CD009885).
- 9.12. The Committee noted that the applicant had requested funding of one or both of two brands of micronutrients, Hardy Nutritionals Daily Essential Nutrients (DEN, Nutratek) and EMPowerPlus Advanced (EMP+ Advanced, Truehope) for ADHD. The Committee noted that both products contained a similar mix of vitamins and minerals, in slightly differing quantities by product and over time.
- 9.13. The Committee noted that both DEN and EMP+ Advanced were classified as a dietary supplement at the doses stated on the packaging; however, at the doses used to treat ADHD (12-15 capsules per day in many of the trials) these products would be classified as a medicine as defined in the Medicines Act 1981, because certain ingredients (eg vitamin D) would be administered in quantities commensurate with a prescription classification. The Committee noted that neither DEN nor EMP+ Advanced was registered as a medicine in New Zealand.
- 9.14. The Committee noted that the supporting clinical trials appeared to have used a different formulation of micronutrients than those for which funding was requested, for example EMP+ rather than EMP+ Advanced, or a different product altogether. The Committee noted the applicant's comments to PHARMAC staff that the suppliers relatively frequently

changed the formulation and name of their products. The Committee considered that this raised significant concerns about the applicability of the evidence to products for which funding was now requested. The Committee noted that changes in formulations of micronutrients was of concern should funding of a micronutrient product be progressed, as PHARMAC could not have confidence that the funded product would remain as intended or that the change in formulation would be identified, particularly given the products are not registered.

- 9.15. The Committee noted that a number of the trials were conducted by the applicant's research group. [REDACTED]

[REDACTED].

- 9.16. The Committee noted a number of publications relating to studies conducted in adults with ADHD, including:

- Rucklidge et al. J Atten Disord 2011;15:79-91. This was an 8-week open label pilot trial investigating the effects of micronutrients (EMP+, 15 capsules per day) on behaviour and mood on 14 adults (9 men, 5 women; 18-55 years) with ADHD and severe mood dysregulation who were selected from an ADHD database. Reported side effects were mild and transient and included nausea, headache and rash. The authors reported that significant improvements were noted across informants (self, observer, clinician) on measures of inattention and hyperactivity/impulsivity, mood, quality of life, anxiety, and stress; however, the mean of inattention remained in a clinical range whereas the means on measures of mood and hyperactivity/impulsivity were normalised.
- Rucklidge et al. J Altern Complement Med. 2011;17:1125-31. This was an 8-week open-label study investigating the effects of micronutrients (EMP+, dose not reported) on neurocognitive functioning in 14 adults with ADHD and severe mood dysregulation. A gender- and age-matched control group of 14 non-ADHD adults not taking the formula were assessed on the same tests 8 weeks apart in order to investigate the impact of practice on the results. The authors reported that significant improvement was observed in the ADHD group, but not the control group, across a range of verbal abilities including verbal learning, verbal cognitive flexibility and fluency, and verbal inhibition.
- Rucklidge et al. Br J Psychiatry 2014;204:306-15. This was a double-blind randomised controlled trial in which 80 adults with ADHD were randomised in a 1:1 ratio to 15 capsules per day of either micronutrients (EMP+, n = 42) or placebo (n = 38) for 8 weeks. A total of 44 patients (55%) were self-referred and the remainder were referred by mental health professionals in the community. Treatment response was defined as ≥30% reduction on any of the self-report Conners Adult ADHD Rating Scale (CAARS) DSM-IV subscales or improvements on Clinical Global Impressions-Improvement (CGI-I) – Overall. The Committee noted that the findings of this study appeared to be mixed, for example intent-to-treat analyses showed significant between-group differences favouring active treatment on self- and observer- but not clinician-ADHD rating scales, and object measures of social outcomes differed (the micronutrient group showed greater overall improvement based on the Global Assessment of Functioning [GAF] score but not on the Longitudinal Interval Follow-up Evaluation Range Impaired Functioning Tool [LIFE-RIFT]). The Committee noted that LIFE was considered to be a better tool than GAF as it is a much more structured questionnaire in four domains of social functioning. The Committee noted that there were no between group differences in adverse events.

- 9.17. The Committee noted a number of publications relating to studies conducted in children with ADHD, including:

- Gordon et al. J Child Adolesc Psychopharmacol 2015;25:783-98. This was a 6-month, open-label, on-off-on-off (reversal design) study in 14 children (8-12 years) with ADHD. Following baseline assessment, participants began an 8 week treatment phase with micronutrients (EMP+) titrated up to a maximum dose of 15 capsules/day. Treatment was withdrawn for 4 weeks, reinstated for a further 8 weeks, and then withdrawn for 4 weeks. Participants identified as having trouble swallowing pills completed pill swallowing training. One participant opted to receive EMP+ in powder form. Primary outcomes included the Conners' Parent Rating Scale (CPRS), the CGI, and the Strengths and Difficulties Questionnaire - Parent version (SDQ). Secondary outcomes were mood and global functioning. The authors reported reductions in ADHD symptoms, improved mood and improved overall functioning during the intervention phases, and deterioration in ADHD symptoms, mood and overall functioning during the withdrawal phases.
- Kaplan et al. J Child Adolesc Psychopharmacol 2004;14:115-22. This was an open label trial of micronutrients (an earlier version of EMP+ called 'E.M.Power+') in 11 children with mood and behavioural problems (7 boys, 4 girls; 8-15 years old); 9 completed the trial. Parents completed the Child Behaviour Checklist (CBCL), Youth Outcome Questionnaire (YOQ), and Young Mania Rating Scale (YMRS) at entry and following at least 8 weeks of treatment. Intent-to-treat analyses revealed decreases on the YOQ ( $p < 0.001$ ) and the YMRS ( $p < 0.01$ ) from baseline to final visit. For the 9 completers, improvement was significant on seven of the eight CBCL scales, the YOQ, and the YMRS ( $p$  values from 0.05-0.001).
- Harding et al. Altern Med Rev 2003;8:319-30. This was a 4-week, open-label trial in 20 children (7-12 years) who received either methylphenidate (5-15 mg 2-3 times daily,  $n=10$ ) or micronutrients (multiple vitamin, a multiple mineral, phytonutrients, essential fatty acids and phospholipids (soy lecithin), probiotics, and amino acids;  $n=10$ ). Outcomes were compared using the Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT). The authors reported improvements in both groups with no between-group differences.
- Sinn and Bryan. J Dev Behav Pediatr. 2007;28:82-91. This was a 15-week double-blind, randomised controlled trial in 132 children (7-12 years) with ADHD who received polyunsaturated fatty acids (PUFAs), PUFAs with micronutrients, or placebo. Significant medium to strong positive treatment effects were found on parent ratings of core ADHD symptoms, inattention, hyperactivity/impulsivity, on the CPRS in both PUFA treatment groups compared with the placebo group; no additional effects were found with the micronutrients.

- 9.18. The Committee noted that the side effects of micronutrients appeared minor (including headache and nausea), transient and did not usually result in treatment discontinuation.
- 9.19. The Committee considered that, overall, the quality of the trials was reasonable (reasonable trial design and robust analysis), but the strength was weak. The Committee noted that there were significant limitations with many of the trial designs, for example very low participant numbers and open-label design, which meant that the interpretation of the results of these trials should be treated with caution. The Committee noted that the randomised controlled trials with larger patient numbers were much less likely to show positive effects of micronutrients. The Committee considered it doubtful that blinding of placebo-controlled trials could successfully be achieved, because of the pungent odour of the micronutrient products. The Committee noted an absence of high-quality supporting evidence for the proposed mechanism of action of micronutrients in modifying ADHD, and considered that placebo effects could not be excluded.
- 9.20. The Committee noted that in some of the trials the participants received pill swallowing training as well as reminders to take their capsules. The Committee considered that there was a high probability that in a 'real world' setting patients would receive daily doses less than those administered in the trials because of the high pill burden.

- 9.21. The Committee considered that, for the purposes of PHARMAC's analyses, it would be reasonable to assume a daily dose of 15 capsules; however, the duration of treatment was unclear. The Committee noted that ADHD medications tend to be taken for several years.
- 9.22. The Committee considered that the available evidence suggested that micronutrients may provide a health benefit (versus no treatment) for patients with ADHD and emotional problems, with less side effects than stimulants. However, the Committee considered that, at present, there was insufficiently strong evidence to support a benefit of micronutrients relative to treatments that are currently funded.
- 9.23. The Committee considered that, if funded for ADHD in the absence of any other restrictions, micronutrients would be taken in a high proportion of all patients with ADHD – i.e. in combination with currently funded treatments, in patients who had received insufficient benefit from currently funded treatments, and in patients who had not yet trialled a currently funded treatment. The Committee noted that it would be possible to limit the eligible patient pool, for example restricting applications to paediatricians or psychiatrists, restricting to patients with severe ADHD/hyperkinesis, and/or restricting to patients with poor clinical response to stimulant treatment. The Committee noted that such restrictions would be largely to manage fiscal risk, as there was no particular evidence base to support restrictions of this nature.
- 9.24. The Committee considered that it was unlikely that the use of micronutrients would reduce or delay the use of currently funded treatments, noting that no evidence had been provided to support this.
- 9.25. The Committee noted that many families have a strong desire for "natural" treatments for children, which could potentially result in a very high use of micronutrients if they were funded.
- 9.26. The Committee considered that the use of micronutrients in patients with ADHD would be unlikely to reduce hospital inpatient admissions, noting that patients are not generally admitted to hospital for the treatment of ADHD. The Committee considered that the use of micronutrients could potentially require more doctor visits, particularly in people who are not taking stimulants or atomoxetine, as the micronutrients would need to be prescribed (not only because they are a prescription medicine at the doses used in the trials but because a prescription would be required for funding) and monitored.
- 9.27. Overall, the Committee considered that micronutrients should not be funded for ADHD, noting the lack of high strength evidence for micronutrients, the availability of effective treatments, the high cost of micronutrients relative to currently funded treatments,

## **10. Denosumab for osteoporosis**

### **Application**

- 10.1. The Committee considered a submission from Amgen for the funding of denosumab (Prolia) for the treatment of osteoporosis in postmenopausal women.

### **Recommendation**

- 10.2. The Committee reiterated its previous recommendation (May 2015) and again **recommended** that denosumab be funded subject to Special Authority criteria and Hospital Medicines List restrictions as outlined below for the treatment of osteoporosis in postmenopausal women who have received inadequate benefit from oral treatments and for whom zoledronic acid is contraindicated because of renal impairment, with a medium priority.

**Initial application** from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:

- 1 The patient is a postmenopausal woman with severe, established osteoporosis; and
- 2 Any of the following:
  - 2.1 History of one significant osteoporotic fracture demonstrated radiologically and documented bone mineral density (BMD)  $\geq$  2.5 standard deviations below the mean normal value in young adults (i.e. T-Score  $\leq$  -2.5) (see Note); or
  - 2.2 History of one significant osteoporotic fracture demonstrated radiologically, and either the patient is elderly, or densitometry scanning cannot be performed because of major logistical, technical or pathophysiological reasons. It is unlikely that this provision would apply to many patients under 75 years of age; or
  - 2.3 History of two significant osteoporotic fractures demonstrated radiologically; or
  - 2.4 Documented T-Score  $\leq$  -3.0 (see Note); or
  - 2.5 A 10-year risk of hip fracture  $\geq$  3%, calculated using a published risk assessment algorithm (e.g. FRAX or Garvan) which incorporates BMD measurements (see Note); or
  - 2.6 Patient has had a Special Authority approval for alendronate (Underlying cause - Osteoporosis) or raloxifene; and
- 3 The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes); and
- 4 Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 mL/min; and
- 5 The patient must not receive concomitant treatment with any other funded antiresorptive agent for this condition or teriparatide.

Notes:

- a) BMD (including BMD used to derive T-Score) must be measured using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable.
- b) Evidence suggests that patients aged 75 years and over who have a history of significant osteoporotic fracture demonstrated radiologically are very likely to have a T-Score  $\leq$  -2.5 and, therefore, do not require BMD measurement for treatment with denosumab.
- c) Osteoporotic fractures are the incident events for severe (established) osteoporosis and can be defined using the WHO definitions of osteoporosis and fragility fracture. The WHO defines severe (established) osteoporosis as a T-score below -2.5 with one or more associated fragility fractures. Fragility fractures are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture (minimal trauma). The WHO has quantified this as forces equivalent to a fall from a standing height or less.
- d) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
- e) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: risedronate sodium tab 35 mg once weekly; alendronate sodium tab 70 mg or tab 70 mg with cholecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialled so that the patient achieves the minimum requirement of 12 months' continuous therapy

- 10.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

## Discussion

- 10.4. The Committee noted that it had reviewed an application from Amgen to fund denosumab for postmenopausal women with osteoporosis at its May 2012 meeting, and had recommended that the application be declined pending further information about the long-term safety of treatment with denosumab. The Committee noted that in July 2014, the Endocrinology Subcommittee of PTAC requested that PTAC re-review denosumab in light of the availability of longer-term safety data, and that Amgen subsequently provided additional information for review.

- 10.5. The Committee noted that it had reviewed the additional information from Amgen in May 2015 and had recommended that denosumab be funded for the treatment of osteoporosis in postmenopausal women who have received inadequate benefit from oral treatments and for whom zoledronic acid is contraindicated because of renal impairment, with a medium priority. The Committee noted its previous comments that it would be reasonable to restrict denosumab to this patient group based on cost and that, under such restrictions, the number of denosumab patients could be very large, potentially more than 10% of the total treated patient population.
- 10.6. The Committee noted that Amgen subsequently provided a response to the May 2015 PTAC minutes, querying the estimated patient numbers under the proposed restrictions, and proposing two potential alternate restrictions: the first would remove the requirement that a patient must have a contraindication to zoledronic acid, and the second would require patients to either experience one symptomatic new fracture after at least 12 months' continuous treatment with an antiresorptive agent or to be contraindicated to zoledronic acid and oral bisphosphonates.
- 10.7. The Committee noted that the criteria it recommended in May 2015 would effectively limit access to denosumab to patients with renal impairment. The Committee noted that PHARMAC staff were seeking further information about the use of osteoporosis treatments in patients with renal impairment.
- 10.8. The Committee noted that in case reports with intravenous bisphosphonates, acute tubular necrosis, and collapsing focal segmental glomerulosclerosis have been reported and in 2009 a US FDA post-market safety review identified five deaths from acute renal failure following zoledronate infusion. A follow-up review in April 2011 showed an additional 11 cases of fatal acute renal failure and nine cases of renal injury requiring dialysis so a safety announcement was published advising zoledronate is contraindicated in patients with creatinine clearance <35 ml/min. (<http://www.fda.gov/Drugs/DrugSafety/ucm270199.htm>)
- 10.9. The Committee noted that the case for renal impairment as a contraindication for using oral bisphosphonates is less clear-cut. Bisphosphonates are renally excreted with low oral bioavailability and a very long terminal half life reflecting release from the skeleton. The Committee noted the information on the alendronate Medsafe Data Sheet: "Medicine that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function".
- 10.10. The Committee noted that, patients with renal impairment were generally excluded from pivotal oral bisphosphonate trials, some trials used serum creatinine as a marker for renal impairment in their elderly subjects and, as a consequence, included a number of people with low creatinine clearance in their analyses.
- 10.11. The Committee noted the publication from Jamal et al (J Bone Miner Res 2007;22:503-8), which reported an analysis of women participating in the Fracture Intervention Trial (FIT), a four year randomised controlled trial of alendronate versus placebo in 6458 participants. Of these, 581 (9.9%) had a severely reduced eGFR (<45 ml/minute). Alendronate was as effective at increasing BMD and preventing vertebral fractures in patients with impaired renal function, and there were no differences in rates of adverse events, by renal function. There was no differential increase in serum creatinine, nor was there an increase in the incidence of severe or renal related adverse events compared with women with a normal eGFR.
- 10.12. The Committee noted a post-hoc analysis of 8996 post-menopausal women with osteoporosis received risedronate or placebo in nine trials reported by Miller et al (J Bone

Miner Res 2005;20:2105-15). A total of 7% (n=572) of participants had eGFR 15-30 ml/min and no signs of renal osteodystrophy as measured by serum PTH and ALP. Two further subgroups were studied (eGFR 30-50ml/min and eGFR>50ml/min). There was no increase in incidence of kidney-related adverse effects in this nor other sub-groups compared to placebo and no cases of osteonecrosis of the jaw. In all three subgroups risedronate significantly increased BMD and reduced vertebral fractures compared to placebo.

- 10.13. The Committee noted the report from Shih et al (Kid Int 2012;82:903-8) of a Canadian population-based cohort study of 18,286 people discharged from hospital following an osteoporotic fracture on oral bisphosphonates, which found no increase in incidence of acute kidney injury, nor rise in serum creatinine, over 90 days compared with those discharged on no bisphosphonate.
- 10.14. Members noted that oral bisphosphonates for secondary prevention of osteoporotic fractures appear to be used in routine clinical practice in New Zealand in patients who have renal impairment. This includes patients receiving dialysis where benefit is judged to outweigh risk.
- 10.15. The Committee noted that the available evidence supported the safety of denosumab in patients with renal impairment. The Committee noted the report from Block et al (J Bone Miner Res 2012;27:1471-9), an open-label, single dose, outpatient study conducted in 12 centres in the US which studied the pharmacokinetics and pharmacodynamics of denosumab in 55 subjects with renal function ranging from normal to ESRF requiring dialysis. Renal function impairment was not shown to have a significant effect on either the pharmacokinetics or pharmacodynamics of denosumab. Hypocalcaemia, extremity pain and nausea were the most common adverse events.
- 10.16. The Committee noted that 73 (of a total of 3935) patients with eGFR<30ml/min were included in the denosumab arm of the pivotal FREEDOM study without resulting in adverse renal or other events compared to subjects with normal renal function (Jamal et al J Bone Miner Res 2011;26:1829-35).
- 10.17. Overall, the Committee considered that there is good evidence that denosumab is safe to use in patients with renal failure, for whom zolendronate is contraindicated. The Committee considered that there is some evidence of moderate quality that risedronate and alendronate are safe in the setting of renal impairment, but the lower limit of creatinine clearance at which to stop using these oral bisphosphonates is uncertain at present.
- 10.18. The Committee noted that Amgen had provided a poster presented at the American College of Rheumatology Meeting in 2015 (Miller et al 2015;Abstract 898). This was an international, multi-centre, double blind double-dummy randomised trial comparing denosumab (n=321) with zoledronic acid (n=322) in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. Thirty-seven percent of patients in each group had had a previous osteoporotic fracture. The primary endpoint was change from baseline in lumbar spine BMD at 12 months. This was a non-inferiority endpoint. Secondary endpoints were change from baseline in total hip and lumbar spine BMD at 12 months. Exploratory endpoints were change from baseline in femoral neck and 1/3 radius BMD at 12 months and change in bone turnover markers in a subset of patients. If the primary efficacy endpoint achieved non-inferiority, secondary endpoints were then tested sequentially to maintain the overall type 1 error rate at 5%. Significantly greater BMD gains were reported with denosumab compared with zoledronic acid and greater reductions in bone turnover markers were seen in the denosumab arm. The Committee noted that this was consistent with previous studies but noted that it was uncertain whether these surrogate endpoint gains translate into clinically significant outcomes. The Committee noted the limitations inherent in making conclusions from data from an unpublished trial.

- 10.19. Taking into account the denosumab trials reviewed previously (May 2015 and May 2012), the Committee considered that there is good evidence from well-conducted high quality clinical trials that denosumab is superior to placebo at reducing the risk of vertebral, non-vertebral and hip fractures in postmenopausal women. The Committee considered that there is also good evidence that denosumab is superior to funded alternatives (alendronate, risedronate and zoledronic acid) at improving surrogate endpoints (increased BMD, reduced bone turnover markers), but the Committee noted that there is no evidence from head to head studies that this translates into reduced fractures. The Committee noted that it was not aware of studies where denosumab was used after zoledronate, although there is evidence that BMD is increased, and bone turnover makers reduced, with denosumab after transitioning from alendronate (Kandler et al. J Bone Miner Res 2010;25:72-81).
- 10.20. The Committee noted its previous (May 2015) comments that hip fractures are associated with significant morbidity and mortality, which has been extensively documented, including in the New Zealand setting. The Committee noted that quality-of-life data obtained in patients with osteoporotic fractures show that loss of quality of life is more severe in patients after hip or multiple vertebral fractures than in patients with a single vertebral fracture or distal radius fracture (Lips et al, Osteoporosis Int 2005;16:447-55). The longer after the fracture, the more quality of life improves, but quality of life is not completely restored.
- 10.21. The Committee considered that some quality of life loss is likely for primary caregivers of people who have osteoporotic fractures, hip fractures in particular. The Committee noted that this is described but not quantified in the “Burden of Osteoporosis in NZ” report by Brown et al 2007. The Committee noted that the majority of patients following hip fracture are discharged to their own home (approximately 70% in an audit from Auckland City Hospital as reported by Fergus et al N Z Med J. 2011;124:40-54) which can place significant burden on primary caregivers.
- 10.22. The Committee noted the report from Christakis et al N Engl J Med 2006;354:719-30 which found that the risk of death for men after hospitalisation of a spouse with a hip fracture was increased hazard ratio, 1.15; (95% CI, 1.11 1.18) and this was similar for women. The Committee noted that “Helping family is confining”, “changing personal plans” and “family adjustments” were identified as the most common “care-giver strains” in a 1999 paper examining caregiver stress caring for people after hip fracture (Saltz et al, J Gerontol Social Work 1999; 30:3-4, 167-181).
- 10.23. Members noted that Māori and Pacific peoples have less osteoporotic fracture incidence than NZ Europeans but that the approach of whānau to care of older Maori after hip fracture may mean that residential care is less likely to be used which might place significant levels of stress on whanau, where culturally they need to be present and may need to learn to care for their kaumatua while they rehabilitate.
- 10.24. Whilst the Committee considered that caregivers and whānau are likely to be significantly affected by a relative experiencing hip fracture, the Committee considered that the precise magnitude of the burden on whānau of patients with osteoporosis is uncertain.
- 10.25. The Committee noted that a number of older adults cannot tolerate oral bisphosphonates, particularly the gastrointestinal side effects and the need to be upright for 30min after taking the dose. The Committee noted that many of these patients are transferred to zoledronate or are left without bisphosphonate treatment, particularly in the setting of renal impairment. The Committee considered that for this particular group the health need is moderately severe. The Committee noted that older adults with polypharmacy in residential care may at times be inappropriately treated with bisphosphonates, or these treatments may not be appropriately discontinued.

- 10.26. The Committee reiterated its previous view that the patient group who would most benefit from denosumab would be those patients who had not responded adequately to oral treatments and who could not take zoledronic acid because of renal impairment.
- 10.27. The Committee considered that renal impairment is unlikely to be a major contributor to whether or not a patient is admitted to residential care following a fracture, noting that admission to residential care following a fracture is likely due to a multitude of inter-related clinical, psychosocial and family reasons. Dementia, frailty, and co-morbidities particularly play a part, as does deconditioning, peri-operative complications, in-hospital illnesses, poly-pharmacy and carer capability/support.
- 10.28. The Committee considered that, for the purposes of PHARMAC's analyses, it would be reasonable to include an increased relative risk of death associated with a Stage 4 kidney disease in the cost utility analysis. However, the Committee noted that creatinine levels can be low in elderly patients who are light (e.g. 50 kg), so it can be challenging to diagnose Stage 4 kidney disease in the elderly.
- 10.29. The Committee considered that the subcutaneous mode of administration of denosumab may be useful for clinicians, patients and families, particularly in situations where the oral tablets aren't tolerated. The Committee considered that, given that denosumab is given every 6 months, it is likely that it would be administered by a Practice nurse in the GP clinic or a district nurse in the home for second or subsequent injections. The Committee noted that there would be a cost to the health system associated with this, also noting that there would be costs associated with monitoring of serum calcium levels.
- 10.30. The Committee considered that the supplier's estimate of patient numbers who would be eligible under the criteria proposed by PTAC is reasonable; i.e. approximately 510 patients who have had a fracture on oral treatment and who have creatinine clearance <30ml/min. Similarly, the Committee considered that the supplier's estimate of the number of patients who could be prescribed denosumab if it was available funded for people who sustained a fracture after zoledronic acid was reasonable. However, the Committee considered that the supplier had underestimated the number of patients who could access denosumab if it was restricted to people who had sustained a fracture on 12 months antiresorptive agents or bisphosphonates were contraindicated. The Committee considered that an "inability to stand or sit upright for at least 30 minutes" contraindication would mean that significantly larger numbers would transition to a 6-monthly subcutaneous injection.
- 10.31. The Committee noted that, unlike bisphosphonates and zoledronate in particular, denosumab needs to be taken continuously in order for benefits in BMD to be maintained, so treatment could potentially be life long.
- 10.32. The Committee noted that although the current treatment algorithm, i.e. oral bisphosphonates moving to zoledronic acid then teriparatide (or denosumab if funded), is similar to international guidelines (e.g. NICE), it is possible that patients would continue to derive clinical benefit from oral bisphosphonates even if they experience a fracture on treatment.

## 11. Sapropterin for phenylketonuria and hyperphenylalaninaemia

### Application

- 11.1. The Committee considered a submission from Te Arai BioFarma for the funding of sapropterin for the treatment of hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency.

### Recommendation

- 11.2. The Committee **recommended** that sapropterin be funded for the treatment of hyperphenylalaninaemia due to phenylketonuria (PKU) in women who are planning to

become pregnant, or are pregnant, and where dietary phenylalanine restriction has been inadequate, with high priority. The Committee also recommended PHARMAC seek advice from the National Metabolic Service regarding possible Special Authority criteria for this patient group and the Committee review this information at a future PTAC meeting.

- 11.3. The Committee **recommended** that sapropterin for the treatment of hyperphenylalaninaemia due to PKU in non-pregnant PKU patients be declined.
- 11.4. The Committee **recommended** PHARMAC consider broadening the range of dietary options of PKU supplements available on the Pharmaceutical Schedule.
- 11.5. The Committee **recommended** sapropterin for the treatment of hyperphenylalaninaemia due to tetrahydrobiopterin (BH4) deficiency be considered on an individual patient basis via the Named Patient Pharmaceutical Assessment (NPPA) policy.
- 11.6. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### **Discussion**

- 11.7. The Committee noted the funding application for sapropterin included several different indications; treatment of hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) in all patients, HPA due to PKU in pregnant women, and HPA due to tetrahydrobiopterin (BH4) deficiency.
- 11.8. The Committee noted sapropterin, a synthetic preparation of BH4, is an oral treatment indicated for the treatment of HPA in sapropterin-responsive adult and paediatric patients with PKU or BH4 deficiency. Members noted in New Zealand sapropterin is available under the brand, Kuvan from another supplier and is Medsafe approved. Members noted that the Kuvan brand is a dispersible tablet that can be dissolved in water and this enables small part doses if needed. Te Arai BioFarma has indicated it could supply a generic version of sapropterin and intends to submit to Medsafe in 2016.
- 11.9. The Committee considered the evidence regarding phenylalanine reduction in patients with PKU submitted with the application to be of low quality and moderate strength. The Committee considered the evidence regarding use of sapropterin in pregnancy for patients with PKU or BH4 deficiency to be of low quality and low strength. Members identified a number of additional references that were not provided in the application.
- 11.10. The Committee noted there is evidence of a threshold effect of phenylalanine levels of >400 micromol/L and an association with an IQ < 85 and this supports the therapeutic practice of targeting a phenylalanine level between 120 and 360 micromol/L (Camp et al. Mol Genet Metab 2014;112:87-122).

### **PKU**

- 11.11. The Committee noted that the incidence of PKU in New Zealand is reported to be 1/15,000 births per year (Frank et al. NZMJ 2007;120:43-52). Members noted PHARMAC dispensing claims data indicates that in the 2015 financial year, 94 patients had been dispensed PKU supplements of which 66 patients were dispensed these supplements on a regular basis. 27% of patients were under 10 years of age and 52% were under 20 years. Members considered there would be around 5 new patients diagnosed with PKU each year.
- 11.12. The Committee noted screening for PKU occurs as part of the national Newborn Metabolic Screening programme. Members noted the mainstay of dietary management for patients with PKU consists of phenylalanine restriction, as well as the use of PKU special foods (amino acid products without phenylalanine) to supplement the patient's intake of other essential amino acids.

- 11.13. The Committee noted a New Zealand qualitative study of eight individuals with PKU indicated the restrictive diet required for the management for PKU can be problematic. Preparation of food can be difficult and time consuming, palatability is an issue and the available range of supplements is limited. Members noted that in general, as individuals with PKU age, adherence to the diet decreases (Koch et al. J Inherit Metab Dis 2002;25:333–46). The Committee questioned whether patients would adhere to medication, if they did not adhere to dietary restrictions.
- 11.14. Members considered this condition can have a significant impact on the patient and their family. Members noted a cross-sectional study of 89 parents in Germany reported self-reported measures of parental quality of life, family stress, social support and parental coping with children with PKU (Fidika et al. Health Qual Life Outcomes 2013;11:54-63). Family stress and perceived social support were powerful predictors of parental quality of life, however overall the parents perceived the quality of life of their children and family positively.
- 11.15. The Committee noted that approximately 20-30% of patients with PKU reportedly respond to sapropterin treatment. Members noted there is no standard criteria to define responsiveness to sapropterin, however a 30% reduction in blood phenylalanine levels is commonly used (Camp et al. Mol Genet Metab 2014;112:87-122). Other possible criteria include increases in dietary phenylalanine tolerance and improved psychological outcomes.
- 11.16. The Committee noted a double-blind randomised, placebo-controlled study (RCT) of sapropterin efficacy in increasing phenylalanine tolerance in children with PKU (Trefz et al. J Pediatr. 2009;154:700-7). Part 1 screened for sapropterin response in 90 patients (serum phenylalanine concentration  $\leq$ 300 micromol/L at day 8 and a reduction of  $\geq$ 30% compared with day 1). In part 2, the 46 responder patients were randomised (3:1) to sapropterin 20mg/kg/day or placebo for 10 weeks while continuing on a phenylalanine restricted diet. After 3 weeks, a dietary supplement was added every 2 weeks if phenylalanine control was adequate. Eligible patients were between 4 to 12 years of age, had PKU with phenylalanine hydroxylase (PAH) deficiency, an estimated phenylalanine tolerance of  $\leq$ 1000mg/day, and were on a restricted diet (serum phenylalanine levels  $\leq$ 480 micromol/L). The primary efficacy endpoint was the amount of daily phenylalanine supplement tolerated by the sapropterin group at week 10 compared with week 0. The week 10 mean (SD) phenylalanine supplement tolerated by patients treated with sapropterin was 20.9 (15.4) mg/kg/day, a significant improvement from the baseline of zero, ( $p<0.001$ ), versus 2.9 (4.0) mg/kg/day in the placebo group ( $p=0.027$ , statistically significant, but of uncertain clinically benefit). The authors concluded these results may allow a subset of patients with PKU increase intake of dietary protein and reduce the need for phenylalanine free protein supplements and still achieve adequate control of serum phenylalanine concentrations.
- 11.17. The Committee noted a Phase III double-blind RCT of sapropterin over 6 weeks in 89 responders to sapropterin identified in a screening study in patients with PKU (Levy et al. Lancet 2007;370:504-10). At 6 weeks, 18/41 (44%) patients given sapropterin (95% CI 28–60) and 4/47 (9%) controls (95% CI 2–20) had a blood phenylalanine reduction of 30% or more from baseline ( $p=0.0002$ ). Blood phenylalanine concentration was reduced by 50% or more in 13/41 (32%) patients who received sapropterin (95% CI 18–48) and 1/47 (2%) controls (95% CI 0–11). Members noted 11/47 (23%) patients in the sapropterin group and 8/41 (20%) in the placebo group experienced adverse events and 82% compliance with treatment was reported.
- 11.18. The Committee noted a 2015 Cochrane review of sapropterin in PKU (Somaraju et al. Cochrane Database Syst Rev 2015;3:CD008005) concluded there was evidence to suggest that treatment with sapropterin could lower blood phenylalanine concentration and improve protein tolerance in individuals with PKU who are responsive to sapropterin. However, the review considered there to be a lack of data on the effectiveness of the treatment on intelligence, growth and quality of life and in people with severe PKU.

- 11.19. The Committee noted an RCT of sapropterin to treat ADHD symptoms and executive function impairment in 118 children and adults with sapropterin-responsive PKU (Burton et al. Mol Genet Metab 2015;114:415-24). 38 patients had ADHD symptoms prior to treatment. Members noted sapropterin therapy resulted in no significant improvement in the primary outcome of Total Score on the ADHD Rating Scale (RS), completed by parents of child/adolescent participants, or adult ADHD Self-Report Scale completed by adult participants, compared with placebo.
- 11.20. The Committee noted six open-label or retrospective studies (Burton et al. Mol Genet Metab. 2011;103:315-22; Lee et al. Am J Med Genet 2008;146A:2851-9; Kiel S et al. Paediatrics 2013;131:1881-8; Longo et al. Mol Genet Metab 2015;114:557-63; Longo et al. Genet Med 2015;17:365-73; Rohr et al. Mol Genet Metab 2015;114:25-8) reported long-term efficacy and safety data of sapropterin in patients with PKU.
- 11.21. The Committee noted that quality of life estimates were reported but that these were from overseas settings where there is better access to palatable PKU supplements. This access to palatable treatment may improve adherence and thus report a higher quality of life than would be expected in the New Zealand population.
- 11.22. The Committee considered if sapropterin was available to patients with PKU then all patients would need to have a trial, and only 20-30% would be sapropterin responsive. Members considered there would be significant fiscal risk associated with funding sapropterin for the entire PKU population. The Committee considered that it would be preferable to have more funded dietary options with PKU supplements available for this group compared with sapropterin treatment.

#### *PKU & Pregnancy*

- 11.23. The Committee noted that women with PKU who are pregnant or those who are planning to become pregnant would have a higher health need for an alternative treatment to manage HPA. Members noted the teratogenic effects of in utero exposure to elevated phenylalanine on the developing foetus (termed maternal PKU or MPKU) include microcephaly, poor foetal growth, congenital heart defects, non-familial facial features and intellectual disability. Members noted the importance of controlled HPA early and throughout pregnancy and the best outcomes in offspring are in women with blood phenylalanine levels of 120–360 micromol/L before conception (Camp et al. Mol Genet Metab 2014;112:87-122, and Feillet et al. JIMD 2014;37:753-62).
- 11.24. Members noted protein needs increase 50% during pregnancy and inadequate protein/energy intake during pregnancy leads to increased phenylalanine levels due to muscle catabolism. The Committee considered dietary control would be the first line treatment in women with PKU planning to become pregnant, however noted that this may not be palatable to some patients who have not previously required dietary control. Members noted sapropterin has been used successfully in pregnant women in conjunction with dietary phenylalanine restriction and PKU supplements (Feillet et al. JIMD 2014;37:753-62, and Grange et al. Mol Genet Metab 2014;112:9-16).
- 11.25. The Committee noted there is limited evidence supporting use of sapropterin during pregnancy, but also noted there were some concerns regarding sapropterin use during pregnancy. Members noted the FDA category for sapropterin is risk category C. The Committee noted there was no evidence of teratogenicity in rats of oral doses of sapropterin (up to 40mg/kg/day) or in rabbits (up to 600mg/kg/day) (Camp et al. 2014). Doses 3-10 times clinical doses resulted in reduced birth weight and litter size in rates with increased cerebral and facial malformations in rabbits (Rev Prescribe 2010;30:102-5). The Committee noted the PKU MOMS registry reported data on 21 pregnancies in women with PKU treated with sapropterin (Grange et al. Mol Genet Metab 2014;112:9-16). The mean phenylalanine level for those women on treatment was 23% lower and better controlled. 75% of pregnancy outcomes were normal for those with a median phenylalanine level <360 micromol/L vs. 40% when levels were >360 micromol/L.

- 11.26. The Committee considered Special Authority criteria could be developed to enable prompt access to sapropterin to women with PKU who are planning to become pregnant. Members considered the National Metabolic Service should have input into developing such criteria, including the duration of treatment pre and post pregnancy.

*BH4 deficiency*

- 11.27. The Committee noted tetrahydrobiopterin (BH4) is an essential cofactor in the conversion of phenylalanine to tyrosine via PAH, the enzymatic biosynthesis of nitric oxide and in the pathways of several neurotransmitters. Members noted high levels of phenylalanine in the brain due to untreated BH4 deficiency are severely neurotoxic, and lead to mental retardation and developmental defects. Members noted infants with BH4 deficiency appear normal at birth, but medical problems ranging from mild to severe become apparent over time. Signs and symptoms of this condition can include intellectual disability, progressive problems with development, movement disorders, difficulty swallowing, seizures, behavioural problems, and an inability to control body temperature. Members considered people with BH4 deficiency have a very high health need.
- 11.28. The Committee noted BH4 deficiency is a rare disorder with an estimated prevalence of 0.5-2 per million people. Members noted there is only one patient currently receiving funded treatment with sapropterin for BH4 deficiency in New Zealand via NPPA.
- 11.29. The Committee noted there is no randomised controlled trial evidence for sapropterin in BH4 deficiency, with evidence limited to observational retrospective registry data. The Committee noted a study by Shintaku et al (Brain Dev 2013;35:406-10) which assessed the long-term efficacy and safety of sapropterin granules in 19 patients with BH4 deficiency in who treatment was initiated before 4 years of age. The average duration of therapy was 13.2 years (maximum 28 years). Members noted the observation that all patients with BH4 deficiency appeared to have good control of serum phenylalanine levels with sapropterin alone, with no need for restrictive diet therapy, indicating that sapropterin therapy could improve patients' quality of life. No patients stopped treatment due to adverse events. One patient experienced seizures and one patient developed increased muscle tone.
- 11.30. The Committee noted a case series of 40 patients with BH4 deficiency in China (Han et al. Brain Dev 2015;37:592-8). Members noted initial dosing was 2mg/kg/day, adjusted to keep blood phenylalanine concentration <120 micromol/L. Patients maintained these levels without a phenylalanine restricted diet, and also received L-dopa and serotonin supplementation. Developmental quotient (DQ) / Intellectual quotient (IQ) records were assessed for 19 patients. No development delay was observed in 9 patients. Of the 10 patients with development delay, 8 patients were diagnosed within the first 2 months of life. Members noted there was no reporting on patient adherence and the impact of the cost of treatment in relation to patient outcomes.
- 11.31. The Committee noted an observational multicenter registry from Europe (KAMPER) reporting 1 year data (Trefz et al. JIMD Rep. 2015;23:35-43) in patients with PKU responsive to sapropterin. Overall 325 patients were analysed, 296 (91.1%) patients with BH4-responsive phenylalanine hydroxylase (PAH) deficiency and 29 (8.9%) with BH4 deficiency. 12 month data was available for 164 patients with PAH and 16 patients with BH4 deficiency. Two patients discontinued treatment, one a non-responder and the other becoming pregnant. Members noted the median dose of sapropterin was higher in the PAH group (12.7mg/kg/day (10.0-18.9) compared to 5.0mg/kg/day (3.0-7.5) in the BH4 group. The primary endpoint was to assess long-term safety and adverse effects associated with sapropterin treatment. The authors concluded no new safety concerns were identified as of May 2013. PTAC members noted bone density was assessed in 59 patients with 2 reported cases of osteopenia and 1 case of osteoporosis. The Committee noted the median dietary phenylalanine intake was higher at 12 months than baseline for all age groups, including adults.

- 11.32. The Committee noted a retrospective, multicentre, chart review of 256 patients with BH4 deficiency across mainland China born between 1985-2010 (Ye et al. JIMD 2013;36:893-901). 194 of 256 (75.8%) patients received sapropterin treatment. Members noted the median starting age for sapropterin therapy decreased from 87.0 months in children born 1985–1999 (n=11), to 25.0 months in those born 2000–2004 (n=14), to 2.0 months in those born 2005–2010 (n=35). Members noted there was a large amount of missing data. Median IQ was 80 in the 33 patients in whom data was reported and the median age at which treatment was started was significantly younger in patients with an IQ above 70 than in patients with an IQ below 70 (2 [CI 1,4] months vs 6 [5,10] months, p=0.02). DQ was available for 59 patients (23%) of which 37 patients had DQ scores within the normal range ( $\geq 85$ ). DQ was negatively associated with age of treatment initiation. Members noted 20 adverse events were reported; diarrhoea and headache were related to sapropterin treatment. There were 17 deaths reported (6.6%) of which 10 were considered due to BH4 deficiency (8 patients receiving no treatment and 2 receiving late treatment).
- 11.33. The Committee considered patients with BH4 deficiency would benefit from sapropterin treatment and there was no suitable alternative treatment, however the number of patients with BH4 deficiency would be extremely small and therefore consideration via the NPPA Policy might be the most appropriate mechanism to consider funding for these patients.