

PTAC meeting held 14 & 15 February 2013

(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 2008*.

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.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

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.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) to:

- (i) enable PHARMAC to protect the privacy of natural persons, including that of deceased natural persons (section 9(2)(a)).

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1 Record of PTAC meeting held November 2012

1.1 The Committee reviewed the minutes of the PTAC meeting held on 8 and 9 November 2012 and made the following amendments:

1.1.1 Paragraph 4.9.3: The Committee suggested that the Special Authority for erythropoietin for myelodysplasia be replaced with the following:

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 months for applications meeting the following criteria:

1. Patient has a confirmed diagnosis of myelodysplasia (MDS); and
2. Has had symptomatic anaemia with haemoglobin <100g/L and is red cell transfusion-dependent*; and
3. Patient has very low or low risk MDS based on the WHO classification-based prognostic scoring system for myelodysplastic syndrome (WPSS) ; and
4. Other causes of anaemia such as B12 and folate deficiency have been excluded; and
5. Patient has a serum erythropoietin level of <500 IU/mL; and
6. The minimum necessary dose of erythropoietin would be used and will not exceed 80,000 iu per week.

Renewal application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

1. The patient's transfusion requirement continues to be reduced with erythropoietin treatment; and
2. Transformation to acute myeloid leukaemia has not occurred; and
3. The minimum necessary dose of erythropoietin would be used and will not exceed 80,000 iu per week.

*Transfusion dependence is defined as a transfusion requirement of at least 4 units of red cells per month over a period of 4 months.

1.1.2 Paragraph 9.14: The Committee suggested the following changes to the proposed Special Authority criteria for Preservative Free Prednisolone Sodium Phosphate:

- Initial Application, point 1: change *Patient has severe inflammation* to *Patient has severe ocular inflammation where steroid eye drops are appropriate*.

1.1.3 Paragraph 13.2:

- Change biological treatments to anti-TNF biologics.
- Special Authority criteria – change *doses* to *months* in both initial and renewal criteria

Special Authority:

Initial application – any relevant practitioner. Approvals valid for three **months** for applications meeting the following criteria:

1. Patient has pyoderma gangrenosum; and
2. Applicant is a Dermatologist or has confirmed the diagnosis with a Dermatologist; and
3. Patient has received three months of conventional therapy including a minimum of three agents (e.g. prednisone, ciclosporin, azathioprine, or methotrexate) and not received an adequate response

Renewal – any relevant practitioner. Approvals valid for three **months** for applications meeting the following criteria:

1. Patient has shown clinical improvement; and
2. Patient continues to require treatment.

1.1.4 Paragraph 13.10: Change Committed to Committee.

1.1.5 Paragraph 15.3: The Committee considered that this paragraph is an action point.

1.1.6 Paragraph 18: The Committee considered the title of this application should change from “*Melatonin – for primary insomnia in patients aged 55 years or over, secondary insomnia in children/adolescents with neurodevelopmental/psychiatric comorbidities and secondary insomnia associated with dementia*” to “*Melatonin – for primary insomnia in patients aged 55 years or over, secondary insomnia in children and adolescents with neurodevelopmental disorders, and secondary insomnia associated with dementia*”, because no evidence was evaluated for its use in children/adolescents with psychiatric comorbidities.

1.1.7 Paragraph 18.5: The Committee considered that this paragraph is an action point.

2 Subcommittee Minutes

2.1 Anti-Infective Subcommittee – 13 December 2012

2.1.1 The Committee noted and accepted the record of the meeting.

2.2 Cancer Treatments Subcommittee – 5 October 2012

2.2.1 The Committee noted and accepted the record of the meeting in relation to items 1-6 and 8-11.

2.2.2 Regarding item 7, the Committee considered that it needed to review the application for Nilotinib for Chronic Myeloid Leukaemia (CML) before it made an official recommendation.

2.2.3 Regarding item 9, the Committee noted that the applicant had provided feedback regarding some specific aspects of the minutes for rituximab in the treatment of 17p deletion CLL. The Committee considered that it would be best for the Cancer Treatments Subcommittee to address these issues, but that these did not impact on PTAC accepting the Subcommittee's recommendation that the application be declined at this point of time.

2.3 Haematology Subcommittee – 6 August 2012

2.3.1 The Committee noted and accepted the record of the meeting in relation to items 1-2, 4 and 5.

2.3.2 Paragraph 2.8: The Committee considered that this paragraph, regarding the widening of access of enoxaparin for the following patient groups, to be an action point:

- Patients with proven intolerance to warfarin;
- Patients with malabsorption syndromes (especially those who have had a small bowel resection);
- Patients who develop thromboses despite adequate anticoagulation with warfarin; and
- Infants who require anticoagulation and treatment with warfarin is not clinically appropriate or practically feasible (especially where the infant is being breastfed).

2.3.3 Regarding item 3, the Committee noted that it had previously recommended that the application for eculizumab be declined; however, the Haematology Subcommittee had recommended it for funding with a low priority. The Committee considered that in light of the Subcommittee's differing recommendation, additional evidence the Haematology Subcommittee had seen and the recent correspondence from the supplier, it would need to re-review all evidence before making a recommendation. The Committee noted the recent public interest regarding eculizumab and considered that a teleconference would ensure a more timely response rather than waiting for the May PTAC meeting. The Committee recommended that PHARMAC staff arrange this meeting for mid to late March and considered that it would be beneficial to have some members of the Haematology Subcommittee present to provide its expert opinion on paroxysmal nocturnal haemoglobinuria and its treatments.

2.3.4 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

2.4 Pulmonary Arterial Hypertension Subcommittee – 4 December 2012

- 2.4.1 The Committee noted and accepted the record of the meeting.
- 2.5 Transplant and Immunosuppressant Subcommittee – 7 September 2012
 - 2.5.1 The Committee noted and accepted the record of the meeting in relation to items 1-3 and 5.
 - 2.5.2 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

3 Matters Arising

- 3.1 Oseltamivir
 - 3.1.1 PTAC noted that the antiviral drugs oseltamivir and zanamivir were proposed to not be included in the Preferred Medicines List. PTAC noted correspondence from a clinician regarding possible inclusion in the PML and an attached NICE recommendation on usage of oseltamivir. Members noted that oseltamivir was being used in many DHB hospitals.
 - 3.1.2 PTAC noted that oseltamivir and zanamivir had been considered as part of the Section H (PML) development process. Members noted that oseltamivir had been recommended not to be included at this time.
 - 3.1.3 PTAC noted the on-going debate between the British Medical Journal and Roche regarding the non-publication of clinical papers relating to oseltamivir. Members noted that up to 70% of papers relating to oseltamivir may not have been released so there could be significant publication bias.
 - 3.1.4 Members noted that no evidence of impact on mortality or morbidity had been presented with respect to oseltamivir.
 - 3.1.5 PTAC noted that if oseltamivir was only available in Hospitals that patients could be sent to hospital emergency departments to access treatment. Members considered that oseltamivir could be restricted to patients in intensive care units and perhaps widened to inpatients considered at high risk of impending need for intensive care. Members considered that oseltamivir should not be used for prophylaxis.
 - 3.1.6 PTAC recommended including oseltamivir on the PML and noted it would define criteria at a later date.
- 3.2 Tocilizumab for Systemic Juvenile Idiopathic Arthritis (sJIA)
 - 3.2.1 The Committee noted that in November 2011 it had recommended that tocilizumab should be funded for the treatment of sJIA subject to access criteria (with clear stopping criteria) restricting its use to patients who have

not responded to prior treatment with non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX) and systemic corticosteroids, with a high priority, subject to Medsafe registration of tocilizumab for sJIA and, preferably, PTAC review of published data from the TENDER trial.

3.2.2 The Committee noted that tocilizumab was now registered for sJIA and that results of the TENDER trial have been published as De Benedetti et al. N Engl J Med 2012;356:2385-95. The Committee was not in a position to review the publication, and this will occur at the next meeting of the Committee in May.

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withheld under s (9(2)(a)) of the OIA

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3.4 Additional Information supplied with PTAC Papers

3.4.1 A member noted that Food and Drug Administration (FDA) review documents and supplementary online files for key trials were particularly helpful when reviewing applications. The Committee agreed that material such as European Medicines Agency (EMA) and FDA reviews should be provided and reiterated that applicants should provide all necessary information (as stated in the 2010 Guidelines for Funding Applications to PHARMAC). Members noted that the Guidelines for Funding Applications (section 6.1) included supplementary clinical information (review articles and published critiques; EMA and FDA reviews, international guidance and assessments by regulatory authorities or health technology assessment agencies), and considered their inclusion in applications should be encouraged by PHARMAC staff. The Committee also considered that PHARMAC should better encourage high quality applications only being submitted.

4 NZRA response to recent minutes

4.1 The Committee reviewed correspondence from the New Zealand Rheumatology Association (NZRA) Executive in response to PTAC's requests for further information on some aspects of the NZRA funding application for rituximab for patients with Anti-Neutrophil Cytoplasm Antibody (ANCA) associated vasculitis (AAV) who are contraindicated or refractory to conventional therapy and clarification on the role of mycophenolate mofetil in the treatment of AAV.

Discussion

- 4.2 The Committee noted the NZRA's correspondence in response to PHARMAC's request for clarification of Special Authority criteria for the funding of rituximab for patients with AAV in regards to the definition of cyclophosphamide contraindication, patient intolerance and disease refractory to conventional treatments.
- 4.3 The Committee noted that the NZRA recommended the following Special Authority criteria for rituximab in AAV:
- 4.3.1 A clinical diagnosis of ANCA associated vasculitis; and
 - 4.3.2 Failure to achieve 'remission' after 3 months of induction therapy with daily oral or pulse intravenous cyclophosphamide. Remission is defined as the complete absence of disease activity for ≥ 6 months whilst receiving immunosuppressive therapy and a daily dose of prednisolone ≤ 7.5 mg; or
 - 4.3.3 Previous cumulative dose of cyclophosphamide >15 g; or
 - 4.3.4 Repeat 3 month induction course of cyclophosphamide would result in cumulative dose >15 g; or
 - 4.3.5 Allergy to cyclophosphamide; or
 - 4.3.6 Women of child bearing age; or
 - 4.3.7 Previous haemorrhagic cystitis; or
 - 4.3.8 Previous urological malignancy; or
 - 4.3.9 Previous haematological malignancy
- 4.4 The Committee noted that the NZRA stated that the definition of remission is based on published recommendations (Hellmich et al. Ann Rheum Dis 2007;66:605-617). The Committee noted that the NZRA also stated that the choice of 15 g as a cumulative dose of cyclophosphamide is based on the approximate dose at which the risk of haematological and urological malignancy significantly increases and is the cut-off recommended by expert opinion.
- 4.5 The Committee recommended that PHARMAC seek further information from the applicant to quantify the risk associated with a cumulative dose of cyclophosphamide >15 g. The Committee recommended that it would be appropriate to list rituximab for AAV restricted by the following criteria and will only confirm this after feedback from the applicant regarding the matter above:
- Initial application** (ANCA associated vasculitis) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
- All of the following:
- 1. Patient has been diagnosed with ANCA associated vasculitis; and
 - 2. MPO-ANCA positive vasculitis has been excluded; and

3. The rituximab dose would not exceed 375 mg/m² of body-surface area per week for a total of 4 weeks; and
4. Any of the following:
 - 2.1 Induction therapy with daily oral or pulse intravenous cyclophosphamide has failed to achieve complete absence of disease after 3 months; or
 - 2.2 Patient has previously had a cumulative dose of cyclophosphamide >15g or a further repeat 3 month induction course of cyclophosphamide would result in a cumulative dose >15g; or
 - 2.3 Patient is allergic to cyclophosphamide and methotrexate is contraindicated; or
 - 2.4 Patient is a woman of childbearing age; or
 - 2.5 Patient has a previous history of haemorrhagic cystitis, urological malignancy or haematological malignancy.

Renewal application (ANCA associated vasculitis) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has been diagnosed with ANCA associated vasculitis; and
 2. Patient has previously responded to treatment with rituximab but is now experiencing in an acute flare of vasculitis; and
 3. The rituximab dose would not exceed 375 mg/m² of body-surface area per week for a total of 4 weeks.
- 4.6 The Committee noted that the NZRA had commented on mycophenolate mofetil (MMF). The Committee noted the two studies provided by the NZRA in relation to MMF: a small randomised trial of 35 patients from China comparing MMF with cyclophosphamide in predominantly MPO-ANCA positive patients (Hu et al. *Nephrol Dial Transplant* 2008; 23(4): 1307-12), and an open label study of MMF in 17 patients with MPO-ANCA vasculitis in a North American population (Silva et al. *Clin J Am Soc Nephrol* 2010; 5(3): 445-53).
- 4.7 The Committee noted the NZRA's view that the phenotype of ANCA vasculitis is very different in Asia compared with European countries and that vasculitis cohort in New Zealand mirrors that of Europe, not Asia. In Asia, >95% of patients with ANCA associated vasculitis are MPO-ANCA positive and have a clinical phenotype of microscopic polyangiitis. Granulomatosis with polyangiitis (Wegener's) or PR3-ANCA positive disease is exceptionally rare and not well represented in the available MMF trials. The Committee noted NZRA comments that in the randomised trial (Hu et al. *Nephrol Dial Transplant* 2008; 23(4): 1307-12) nearly all patients were MPO-ANCA positive and the study excluded patients with organ or life threatening disease, pulmonary haemorrhage, and patients who had had high doses of prior cytotoxic medications (i.e. cyclophosphamide), all settings where the NZRA considered that rituximab would be used clinically.
- 4.8 The Committee noted the NZRA's views that the open label study (Silva et al. *Clin J Am Soc Nephrol* 2010; 5(3): 445-53) of 17 North American patients with MPO-ANCA vasculitis with only renal involvement showed some promising results which possibly suggests that MMF probably also works in Caucasian patients with MPO-ANCA renal vasculitis. The Committee considered that the available evidence for MMF in patients with MPO-ANCA positive vasculitis is as good as that for rituximab in that indication.

For that reason, the Committee considered that it would be appropriate to exclude this patient group from rituximab funding. The Committee however agreed that the evidence base for MMF in other types of AAV is not as good as for rituximab.

- 4.9 The Committee considered that it would be appropriate to leave MMF for vasculitis induction treatment on the priority list because there is evidence for MMF in MPO-ANCA positive vasculitis although rituximab is preferred over MMF for other types of AAV.
- 4.10 The Committee noted that the NZRA was disappointed by PTAC's low priority recommendation for rituximab in patients with AAV who have a contraindication to cyclophosphamide or where their disease has failed to respond to conventional therapy. After considering all the information provided and previously reviewed, the Committee considered that it would maintain its previous recommendation for rituximab to be funded for this indication with low priority.
- 4.11 The Decision Criteria particularly relevant to these recommendations are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

5 Rilpivirine – HIV/AIDS

Application

- 5.1 The Committee reviewed an application from Janssen-Cilag for the listing of rilpivirine on the Pharmaceutical Schedule for the treatment of HIV infection.

Recommendation

- 5.2 The Committee **recommended** that rilpivirine be listed on the Pharmaceutical Schedule only if cost neutral to efavirenz.
- 5.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

- 5.4 The Committee noted that rilpivirine is a Non-nucleoside reverse transcriptase inhibitor (NNRTI), indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment naïve patients. Members noted that the indication for rilpivirine is limited to patients with HIV without pre-existing NNRTI resistance mutation and have HIV viral load $\leq 100,000$ copies per ml.

- 5.5 The Committee noted that there are approximately 2000 people with diagnosed HIV currently residing in New Zealand and that, including undiagnosed patients, the total number of patients with HIV currently residing in New Zealand could be estimated at 2500. The Committee noted that 100-150 new HIV diagnoses are made each year and that the estimated number of HIV infected patient currently on antiretroviral therapy (ART) at the beginning of 2012 was 1603.
- 5.6 The Committee noted that the primary aim of ART was the suppression of HIV replication, resulting in a marked reduction in both mortality and morbidity associated with chronic HIV infection. In achieving this outcome, the minimisation of drug toxicity is an important factor to be taken into consideration.
- 5.7 The Committee noted that the life expectancy for patients with HIV has been stated to be about 13 years less than the general population (May et al. *BMJ* 2011;343:d6016) but that this number may be confounded by other risk factors (Freeberg *BMJ*. 2011;343:d6015). Members noted that that a more recent study comparing life expectancy in those with or without HIV, but with similar risk factors (Helleberg et al. *Clin Infect Dis* 2013;56(5):727-34) reported that the numbers of life years lost with HIV infection may be as low as 5.1 years, when effective ART is used.
- 5.8 The Committee noted evidence from the ECHO trial (Molina et al. *Lancet*. 2011;378(9787):238-46), a phase 3 randomised double-blind, double-dummy, active-controlled trial, in patients infected with HIV-1 who were treatment-naive. The Committee noted that 346 patients were randomly assigned to receive rilpivirine and 344 to receive efavirenz and received at least one dose of study drug, with 287 (83%) and 285 (83%) in the respective groups having a confirmed response at week 48. The point estimate from a logistic regression model for the percentage difference in response was -0.4 (95% CI -5.9 to 5.2), confirming non-inferiority with a 12% margin (primary endpoint). The incidence of virological failures was 13% (rilpivirine) versus 6% (efavirenz; 11%vs 4% by intention-to-treat time-to-loss-of-virological-response (ITT-TLOVR)). Grade 2-4 adverse events were 16% on rilpivirine vs. 31% on efavirenz ($p < 0.0001$), discontinuations due to adverse events 2% on rilpivirine vs. 8% on efavirenz, rash, dizziness, and abnormal dreams or nightmares were more common with efavirenz. Increases in plasma lipids were significantly lower with rilpivirine. Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.
- 5.9 The Committee noted the evidence from the THRIVE study (Cohen et al. *Lancet*. 2011;378(9787):229-37), a 96-week, phase 3, randomised, double-blind, double-dummy, non-inferiority trial It involved adults (≥ 18 years) not previously given antiretroviral therapy and with a screening plasma viral load of 5000 copies per mL or more and viral sensitivity to background NNRTIs. Patients were randomly allocated to receive oral rilpivirine 25 mg once daily or efavirenz 600 mg once daily; all patients received an investigator-selected regimen of background nucleoside reverse transcriptase inhibitors (NRTIs) The primary outcome was non-inferiority (12% margin on logistic regression analysis) at 48 weeks in terms of confirmed response (viral load < 50 copies per mL, defined by the intent-to-treat time to loss of virologic response [TLOVR] algorithm) in all patients who received at least one dose of study drug. There were 340 patients randomised to each group. 86% of patients who received at least one dose of rilpivirine responded, compared with 82% of patients who received at least one dose of efavirenz (difference 3.5% [95% CI -1.7 to 8.8]; p (non-inferiority) < 0.0001).

Increases in CD4 cell counts were much the same between groups. 7% of patients receiving rilpivirine had a virological failure compared with 5% of patients receiving efavirenz. 4% of patients in the rilpivirine group and 7% in the efavirenz group discontinued treatment due to adverse events. Grade 2-4 treatment-related adverse events were less common with rilpivirine 16% than they were with efavirenz 31%; $p < 0.0001$), as were rash and dizziness ($p < 0.0001$ for both) and increases in lipid levels were significantly lower with rilpivirine than they were with efavirenz ($p < 0.0001$).

- 5.10 The Committee noted the TMC278-C204 study (Wilkin et al. AIDS Res Hum Retroviruses. 2012;28:437-46) which was a 96-week trial of rilpivirine in 368 HIV-1-infected, treatment-naive patients, which was extended to investigate long-term safety and efficacy. Week 192 analysis results were presented. This was a long-term follow-up of a Phase IIb, randomized trial. No significant rilpivirine dose-response relationships with respect to the primary endpoint (composite ITT-TLOVR algorithm) were observed at week 48 or 96. All rilpivirine treated patients were switched to open-label 75 mg qd at week 96 and then to 25 mg qd, the Phase III dose, at approximately week 144 as it gave the best benefit-risk balance. All control patients continued receiving open-label efavirenz 600 mg qd. At week 192, 59% of rilpivirine and 61% of efavirenz -treated patients maintained confirmed viral load < 50 copies/ml (ITT-TLOVR algorithm). The mean changes from baseline in CD4 cell count were similar in both groups (rilpivirine: 210 cells/mm³ vs. efavirenz: 225 cells/mm³). No new safety concerns were noted between week 48 and 192. In the week 192 analysis, rilpivirine compared with efavirenz was associated with a lower overall incidence of grade 2-4 adverse events (AEs) at least possibly related to treatment, including rash ($p < 0.001$) and neurologic AEs ($p < 0.05$ Fisher's exact test, post hoc analyses). Incidences of serious AEs, grade 3 or 4 AEs, and discontinuations due to AEs were similar across groups. Increases in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were significantly lower with RPV than with efavirenz.
- 5.11 Members noted that the 96 week data from the TMC278-209 and TMC278-C215 trials was now available on the Food and Drug Administration website and that pooled data from these trials show a 76% HIV RNA < 50 copies with rilpivirine and 77% with efavirenz. In those with baseline HIV viral load $< 100,000$ copies/ml, the percentage < 50 copies/ml at 96 weeks was 82% and 78% respectively.
- 5.12 The Committee noted that rilpivirine had equivalent efficacy to efavirenz when used in those with viral loads $\leq 100,000$ based on the non-inferiority analysis
- 5.13 The Committee noted that the major adverse effects of NNRTI such as neurological, hepatotoxicity and rash were significantly less with rilpivirine and that it may be less likely to cause blood lipid derangements. The Committee noted that rilpivirine is generally better tolerated than efavirenz. The Committee also noted that the impact on the cytochrome P450 was considered less than for efavirenz.
- 5.14 The Committee noted that resistance to rilpivirine likely results in the development of cross resistance to all NNRTI's including etravirine, whereas when resistance to efavirenz and neviraprine developed there was no cross resistance to etravirine. Members noted that the bioavailability of rilpivirine is highly dependent on food and is also varies with gastric pH.

- 5.15 The Committee noted that with regards to a switch strategy, studies were limited. The Committee noted the SPIRIT trial; (presented at XIX International AIDS conference, July 2012). The trial randomised patients to switch to tenofovir/emtricitabine/rilpivirine (n=317) or remain on boosted ritonavir-boosted protease inhibitor based ART (n=157) and showed after 24 weeks 93.7% and 89.9 % of patients remaining virologically suppressed.

6 Long-acting octreotide for metastatic or unresectable SI-NETs without carcinoid syndrome

Application

- 6.1 The Committee considered an application from a group of oncologists for the funding of long-acting octreotide (octreotide LAR) for tumour control until progression in patients with metastatic or unresectable Small Intestinal Neuroendocrine Tumours (SI-NETs) in the absence of carcinoid syndrome.

Recommendation

- 6.2 The Committee deferred making a recommendation on octreotide LAR for SI-NETs without carcinoid syndrome. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee (CaTSoP) for consideration, and in particular for advice on describing any health related quality of life benefit from using octreotide LAR in SI-NET patients without carcinoid syndrome, and whether short acting octreotide could be a viable alternative to octreotide LAR.

Discussion

- 6.3 The Committee noted that short-acting octreotide is available without restriction and that octreotide LAR is funded for patients with SI-NETs with carcinoid syndrome to improve symptoms such as flushing, diarrhoea, bronchospasm and right-sided heart disease. The Committee noted that the use of octreotide in the absence of carcinoid syndrome is not a registered indication in New Zealand.
- 6.4 The Committee noted that the incidence of SI-NETS is about 0.46 per 100,000 population (Neiderle et al. *Endocr Relat Cancer* 2010;17(4):909-18), with about 80% of these being without carcinoid syndrome and 77% of these subgroup of patients having unresectable or metastatic disease. The Committee noted the incidence of patients in New Zealand with metastatic or unresectable SI-NETs without carcinoid syndrome was about 12-13 patients per year, but that prevalence is higher because of the prolonged clinical course of this illness.
- 6.5 The Committee noted evidence from a randomised, double-blind, placebo-controlled trial, the PROMID study (Rinke et al. *J Clin Oncol.* 2009;27(28):4656). Members noted that 85 treatment-naive patients were randomised to either placebo or octreotide LAR 30mg intramuscular injection per month. The primary end point was time to tumour progression or tumour related death. 162 patients were planned to be recruited but recruitment was slow and due to the effects of octreotide on tumour progression noted in interim analysis the trial stopped recruiting and was unblinded after 16 deaths (three

of unrelated causes). The Committee considered it was unclear how tumour progression was determined in the trial.

- 6.6 The Committee noted in the interim intention to treat analysis there were more progressions in the placebo arm; 41 placebo and 26 octreotide (HR = 0.32, 95% CI 0.19 to 0.55, p=0.000015). The median time to tumour progression was 14.3 months for octreotide (95% CI, 11 to 28 months) and 6 months for placebo (95% CI, 3.7 to 9.4 months), HR 0.34; 95% CI, 0.20 to 0.59; p=0.000072. Patients with and without carcinoid treatment responded similarly to treatment, with numbers too small to detect any small difference in outcome. There was no difference in quality of life measures between the groups after the first 6 months of the trial. Members considered there was no evidence of overall survival gains. Serious adverse events occurred in 11 octreotide and 10 placebo patients, including GI tract (octreotide n=6; placebo n=8), the hematopoietic system (octreotide n=5; placebo, n=1), and general health status (fatigue and fever; octreotide n=8; placebo n=2).
- 6.7 The Committee considered a number of uncontrolled observational studies. In a retrospective study of 146 patients with metastatic midgut NETs (Strosberg et al. *Neuroendocrinology* 2009;89:471-476), 91% of patients had received long-term depot octreotide treatment and the overall 5-year survival rate was 75%, compared with 19-55% in historical controls. Members noted that 83% of these patients had carcinoid syndrome.
- 6.8 The Committee noted Di Bartolomeo (*Cancer* 1996;77(2):402-408), an open label uncontrolled study of short acting octreotide in 58 patients with various metastatic neuroendocrine tumours. 23 patients received 500 mcg 3 times a day and 35 patients received 1000 mcg 3 times a day until tumour progression. 53% of tumours were carcinoid and of these 50% had carcinoid syndrome. Tumour regression was seen in 2 carcinoid patients. Longer term treatment with relatively high doses of octreotide stabilised disease for a median duration of 12 months (6-32+ months), although the Committee noted there was no control group to compare with.
- 6.9 The Committee noted Saltz et al (*Cancer* 1993;72(1):244-8), an open label uncontrolled study of short acting octreotide in 20 patients with progressed disease, with doses of 150 to 250 mcg three times daily (median 250mcg three times daily). Median survival on octreotide was not reached by 29 months, which appeared better than historical controls, but the Committee considered this comparison was not definitive.
- 6.10 The Committee noted Leong et al (*J Surg Oncol* 2002,79(3):180-7), being case reports of two patients treated with short acting octreotide 100mcg three times daily for symptomatic control of carcinoid syndrome who had complete macroscopic regression of metastatic lesions.
- 6.11 The Committee noted that other uncontrolled studies were provided, but considered that as these studies in general examined patients with carcinoid syndrome the results were difficult to interpret in relation to patients without carcinoid syndrome.
- 6.12 The Committee considered that overall the strength of the evidence was moderate and the quality was low.

- 6.13 The Committee noted that short acting octreotide is currently available without restriction, while access to funded octreotide LAR is restricted by special authority. The evidence for the use of short acting octreotide is confined to uncontrolled studies and case reports with small numbers, whereas evidence for octreotide LAR is one RCT. The Committee considered that it would be unlikely that more clinical evidence would become available for octreotide in this indication. Members noted the National Comprehensive Cancer Network guidelines (NCCN v1, 2012, Carcinoid Tumors) suggest short acting octreotide SC 150mcg to 250mcg tds or octreotide LAR 20-30mg IM every four weeks for asymptomatic low tumour burden or clinically significant tumour burden, category 2A. The Committee considered these doses to be appropriate.
- 6.14 The Committee noted O'Toole (Cancer 2000;15:88(4):770-6), which compared patient acceptance of two or three times daily 200mcg octreotide injections with lanreotide intramuscular injection every 10 days. 68% of patients preferred lanreotide, largely due to the simplified mode of administration. Members considered that patients will prefer octreotide LAR to the short acting formulation, due to the inconvenience and discomfort of injecting short acting octreotide three times daily. The Medsafe datasheet reports localised pain at the injection site as a very common adverse drug reaction for short and long acting octreotide. Members noted the disutility of frequent pain on injection should be considered in any cost-utility analysis of short acting octreotide. Members also noted that the short acting octreotide is less expensive than octreotide LAR on a dose equivalence basis.
- 6.15 The Committee noted that the gains in quality of life from delaying tumour progression with octreotide for patients without carcinoid syndrome were not apparent from the results of the PROMID trial. Disease stabilisation would offer a longer progression free period. Members noted there was no good evidence of overall survival gains. Members also noted there may be some quality of life reduction due to the side effect profile of both short and long acting octreotide.
- 6.16 The Committee noted there is additional health sector expenditure required with administering octreotide, requiring a baseline ultrasound of the gallbladder prior to commencing treatment and at six monthly intervals thereafter, given that gallstones developed in 15-50% of long term patients (Medsafe datasheet). For octreotide LAR there is also the additional cost of administering the intramuscular injection once a month (where conversely patients themselves are able to subcutaneously self-administer short acting octreotide).
- 6.17 The Committee considered the group of patients with asymptomatic SI-NETs most likely to benefit from treatment with octreotide was patients with resected primary tumours and a low hepatic tumour load (according to explorative analysis in the PROMID trial). Members noted Aparicio et al (Eur J Cancer 2001;37:1014-1019), which examined predictive factors of response in patients with progressive metastatic neuroendocrine tumours (34% had small intestine primary). Stabilisation was more likely in patients with slowly progressive tumours.
- 6.18 The Committee noted that the applicant requested access to octreotide LAR for patients without carcinoid syndrome until disease progression and that any special authority should reflect this. Members also noted a study by Ferolla et al (J Endocrinol Invest. 2012;35(3):326-31) which evaluated a 21 day administration of octreotide LAR

on patients who had progressed on the standard 28 day regime, and which showed some evidence of both increased dose frequencies (hence greater overall usage) and treatment continuing despite disease progression, rather than treatment ceasing at progression. The Committee noted that there was currently insufficient evidence to support this treatment approach and the Special Authority criteria should be worded to exclude octreotide LAR from being used in this way.

7 Fingolimod in Multiple Sclerosis

Application

- 7.1 The Committee reviewed a funding application from Novartis for fingolimod (Gilenya) for the treatment of relapse remitting multiple sclerosis (RRMS) following the receipt of advice relating to the application and possible treatment algorithms from the Neurology Subcommittee July 2012, the Multiple Sclerosis Treatments Advisory Committee (MSTAC) June 2012, and cost utility analysis from PHARMAC staff.

Recommendation

- 7.2 The Committee deferred recommending fingolimod for funding, pending further advice from the Neurology Subcommittee and MSTAC, and requested further analysis by PHARMAC staff as to its cost-effectiveness in the context of a number of possible treatment algorithm models. This includes fingolimod as first line treatment, early treatment commencing at diagnosis (e.g. EDSS less than 2.0), and ceasing treatment at the onset of secondary progressive multiple sclerosis.

Discussion

- 7.3 The Committee noted the minutes relating to the review of fingolimod and of possible MS treatment algorithms from the Neurological Subcommittee and MSTAC.
- 7.4 The Committee noted that a number of scenarios had been considered by MSTAC and the Neurological Subcommittee. It noted both committees had recommended that fingolimod be funded as second line treatment following an adequate trial of at least six months of either interferon or glatiramer or both. MSTAC and the Neurological Subcommittee also recommended that fingolimod be funded as a first line treatment in exceptional cases for patients with highly active rapidly progressive MS.
- 7.5 The Committee considered that the Neurological Subcommittee and MSTAC should give further consideration to the role of fingolimod as a first line agent for all MS patients, and clarify their recommendations bearing this possibility in mind. The reasons for this were discussed as follows.
- 7.6 The Committee considered that a six month trial of first line treatments is unlikely to be sufficient to determine the effectiveness of current treatments, given that the course of the disease can be slowly progressive and relapses can be infrequent. The Committee noted that no clear definition was given of the group with highly active rapidly progressive MS, and considered that there was no evidence to support targeting this subgroup of patients with fingolimod treatment.

- 7.7 The Committee also noted that treatment sequencing was considered within the current Special Authority parameters, where treatment with beta interferon or glatiramer could commence from EDSS 2.0 and if the relapse criteria are met. The Committee considered that if an adequate trial of beta interferon and glatiramer were used first, it is likely that fingolimod would be used later in the course of the disease. In order to have a reasonable trial of fingolimod, access would need to be widened to accommodate this.
- 7.8 The Committee noted the Scafari et al. study (Brain 2010;113;1914-1929) which was cited by the Neurological Subcommittee. The Committee noted that the study used London Ontario registry data with 28,000 patient years observing relapsing remitting MS with disability and death outcomes. The Committee noted that this is considered to provide the best descriptive epidemiology internationally and is widely used to study the course of MS. However the Committee considered the data have some limitations. The Committee noted that Disability Status Scale (DSS) as a key outcome measure used in the Ontario dataset was less precise than more recent Expanded Disability Status Scale (EDSS) metric, DSS scores were determined retrospectively, onset of progression was not considered to begin until DSS 3, measurements assumed no regression of disease and hence automatically discounted improvements in DSS scores, and distinctions between relapse remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) were not well described.
- 7.9 The Committee considered that the Scafari et al. study indicates that the number of relapses in first two years (presumably after diagnosis) and a short gap between the first and second relapses were associated with a higher probability of conversion to SPMS. The Committee noted that fewer relapses from the third year onwards was associated with a greater probability of conversion to SPMS and that the time to DSS 3.0 was highly predictive of time to DSS 6.0, 8.0 and 10.0. The Committee noted that in the context of clinical trials, at baseline, the mean duration of MS (from first symptoms to randomisation) in the FREEDOMS study (Kappos et al. N Eng J Med 2010;362:387-401) was 8 years, and the mean EDSS was 2.3. Bearing this in mind, the Committee considered that many of the patients in the FREEDOMS study would have commenced treatment with fingolimod at a later stage of disease – perhaps when the treatment was less likely to show an effect (i.e. relapse rate was already reducing).
- 7.10 The Committee noted that the total number of relapses does appear to be associated with the risk of progression. The Committee considered that this implies that relapses (except in the first two years) are not clear risk factors for progression of disability and reiterated its earlier view that reducing relapses especially after the first 2 years would not necessarily reduce the risk of progressive decline.
- 7.11 The Committee considered that the Scafari study data raises more uncertainty about when to start and when to discontinue treatment for RRMS. The Committee considered that it could be suggested that reducing the relapse rate early, in the first two years may be of greater clinical value than reducing relapses after the first two years and that treatment would be discontinued earlier at the onset of SPMS.
- 7.12 The Committee considered that, in theory, using fingolimod and a treatment that reduced disease worsening in sequence could be effective in delaying the progression of MS. However, the Committee noted that there is no research evidence to support

this theory, and that concerns remain about the long term safety and cost-effectiveness of fingolimod.

- 7.13 The Committee considered that fingolimod would be associated with a number of additional health sector costs, including the need for heart monitoring for 6 hours following the first dose; ophthalmology review at commencement of treatment, 3 months, then annually; and dermatology review at commencement then annually.
- 7.14 The Committee considered that the assumptions used by PHARMAC in its cost effectiveness modelling to date remained appropriate. The Committee noted that fingolimod showed a small advantage in reducing disability compared with placebo at 24 months in the FREEDOMS trial. However the Committee considered it would be difficult to extrapolate any long terms effect on disease progression as a result of that study.
- 7.15 The Committee considered that based on the TRANSFORMS study (Cohen et al. N Engl J Med 2010), fingolimod is likely to have similar effects on disease progression and reduces relapses by approximately 50% when compared with interferon beta-1-alpha (Avonex).
- 7.16 The Committee considered that the treatment scenarios modelled by PHARMAC staff, including using current treatments (beta-interferon and glatiramer) for a maximum of 2.0 EDSS states followed by fingolimod treatment for a maximum of 2.0 EDSS states showed poor cost effectiveness outcomes.
- 7.17 The Committee noted that it remains unconvinced about the effectiveness of the currently funded treatments for MS and invited the Neurological Subcommittee and MSTAC to consider innovative treatment scenarios which utilise the newer agents that have better evidence of effectiveness. The Committee considered that further advice be sought about whether fingolimod could be considered as first line treatment and on the clinical appropriateness of ceasing treatment at the onset of SPMS (if the entry criteria were amended as recommended by PTAC February 2012).

8 Natalizumab in Multiple Sclerosis

Application

- 8.1 The Committee reviewed a funding application from Biogen Idec for natalizumab (Tysabri) for the treatment of relapse remitting multiple sclerosis (RRMS) following the receipt of advice relating to the application and possible treatment algorithms from the Neurology Subcommittee July 2012 and (Multiple Sclerosis Treatments Advisory Committee (MSTAC)) June 2012 and cost utility analysis from PHARMAC staff.

Recommendation

- 8.2 The Committee deferred recommending natalizumab for funding, pending further advice from the Neurology Subcommittee and MSTAC, and requested further analysis by PHARMAC staff as to its cost-effectiveness in the context of a number of possible treatment algorithm models. This includes natalizumab as first line treatment, early treatment commencing at diagnosis (e.g. EDSS less than 2.0), and ceasing treatment at the onset of secondary progressive multiple sclerosis.

Discussion

- 8.3 The Committee noted the minutes relating to the review of natalizumab and of possible MS treatment algorithms from the Neurological Subcommittee and MSTAC.
- 8.4 The Committee noted that a number of scenarios had been considered by MSTAC and the Neurological Subcommittee. Members noted both committees had recommended that natalizumab be funded as second line treatment following an adequate trial of at least six months of either interferon or glatiramer or both. MSTAC, and the Neurological Subcommittee had also recommended that natalizumab be funded as a first line treatment in exceptional cases for patients with highly active rapidly progressive MS.
- 8.5 The Committee considered that the Neurological Subcommittee and MSTAC should give further consideration to the role of natalizumab as a first line agent for all MS patients, and clarify their recommendations bearing this in mind. The reasons for this were discussed as follows.
- 8.6 The Committee considered that a six month trial of first line treatments is unlikely to be sufficient to determine the effectiveness of current treatments, given that the course of the disease can be slowly progressive and relapses can be infrequent. The Committee noted that no clear definition was given of the group with highly active rapidly progressive MS, and considered that there was no evidence to support targeting this subgroup of patients with natalizumab treatment.
- 8.7 The Committee also noted that treatment sequencing was considered within the current Special Authority eligibility parameters, where treatment with beta interferon or glatiramer could commence from EDSS 2.0 and if the relapse criteria are met. The Committee considered that if an adequate trial of beta interferon and glatiramer were used first, it is likely that natalizumab would be used later in the course of the disease. In order to have a reasonable trial of natalizumab, access would need to be widened to accommodate this.
- 8.8 The Committee noted the Scafari et al. study (Brain 2010;113;1914-1929) which was cited by the Neurological Subcommittee. The Committee noted that the study used London Ontario registry data with 28,000 patient years observing relapsing remitting MS with disability and death outcomes. The Committee noted that this is considered to provide the best descriptive epidemiology internationally and is widely used to study the course of MS. However, the Committee considered the data have some limitations. The Committee noted that Disability Status Scale (DSS) as a key outcome measure used in the Ontario dataset was less precise than more recent Expanded Disability Status Scale (EDSS) metric, DSS scores were determined retrospectively, onset of progression was not considered to begin until DSS 3, measurements assumed no regression of disease and hence automatically discounted improvements in DSS scores, and distinctions between relapse remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) were not well described.
- 8.9 The Committee considered that the Scafari et al. study indicates that the number of relapses in first two years (presumably after diagnosis) and a short gap between the first and second relapses were associated with a higher probability of conversion to SPMS. The Committee noted that fewer relapses from three years onwards was

associated with a greater probability of conversion to SPMS and that the time to DSS 3.0 was highly predictive of time to DSS 6.0, 8.0 and 10.0.

- 8.10 The Committee noted that the total number of relapses does not appear to be associated with the risk of progression. The Committee considered that this implies that relapses (except in the first two years) are not clear risk factors for progression of disability and reiterated its earlier view that reducing relapses especially after the first 2 years would not necessarily reduce the risk of progressive decline.
- 8.11 The Committee considered that the Scafari study data raises more uncertainty about when to start and when to discontinue treatment for RRMS. The Committee considered that it could be suggested that reducing the relapse rate early, in the first two years may be of greater clinical value than reducing relapses after the first two years and that treatment would be discontinued earlier at the onset of SPMS.
- 8.12 The Committee noted that natalizumab appears to be superior to beta-interferon in reducing relapses and in delaying disease worsening. The Committee considered that, in theory, using natalizumab early (before EDSS 2.0) may be associated with better outcomes, however concerns remain about the long term safety and the cost-effectiveness of natalizumab.
- 8.13 The Committee noted that developing progressive multifocal leukoencephalopathy (PML) is a risk for patients with John Cunningham Virus (JCV) antibodies who are using natalizumab. The Committee noted that in JCV antibody positive people, the risk of PML increased for patients with a history of using immunosuppressant MS and in patients who received more than 24 natalizumab infusions (or following 2 years of treatment). The Committee considered that natalizumab would be associated with additional health sector costs as it is a hospital treatment. The Committee noted that monitoring is required for John Cunningham Virus (JCV) antibodies during treatment in order to inform risk assessment for the development of progressive multifocal leukoencephalopathy (PML).
- 8.14 The Committee considered that the assumptions used by PHARMAC in its cost effectiveness modelling to date remained appropriate.
- 8.15 The Committee considered that the treatment scenarios modelled by PHARMAC staff, including using current treatments (beta-interferon and glatiramer) for a maximum of 2.0 EDSS states followed by natalizumab treatment for a maximum of 2.0 EDSS states, showed poor cost effectiveness outcomes.
- 8.16 The Committee noted that it remains unconvinced about the effectiveness of the currently funded treatments for MS and invited the Neurological Subcommittee and MSTAC to consider innovative treatment scenarios which utilise the newer agents that have better evidence of effectiveness. The Committee considered that further advice be sought about whether natalizumab could be considered as first line treatment and on the clinical appropriateness of ceasing treatment at the onset of SPMS (if the entry criteria were amended as recommended by PTAC February 2012).

9 Sevelamer for hyperphosphataemia in adult patients with chronic kidney disease on dialysis

Application

- 9.1 The Committee reviewed an application from Sanofi New Zealand for the funding of sevelamer hydrochloride (Renagel) for the treatment of hyperphosphataemia, in adult patients with chronic kidney disease stage 4 or 5, on dialysis.

Recommendation

- 9.2 The Committee **recommended** that the funding application for sevelamer hydrochloride be declined.
- 9.3 The Decision Criteria particularly relevant to this recommendation are: *(i) the health needs of all eligible people within New Zealand; (iii) the availability and suitability of existing medicines; and (iv) the clinical benefits and risks of the pharmaceutical.*

Discussion

- 9.4 The Committee noted that hyperphosphataemia is a condition commonly associated with chronic kidney disease as a result of the gradual decline in renal phosphate clearance. The Committee noted that hyperphosphataemia is usually prevented by parathyroid hormone and fibroblast growth factor-23 and phosphate levels can be controlled by dietary restriction however during the later stages of CKD, phosphate binding treatments are needed. The Committee noted that the currently funded phosphate binding treatments in New Zealand are calcium or aluminium-based.
- 9.5 The Committee noted that both calcium and aluminium are effective and inexpensive phosphate binders, with the advantage of aluminium being that it does not cause hypercalcaemia.
- 9.6 The Committee noted that safety concerns have been raised for both aluminium and calcium. The Committee noted that in the 1980s, aluminium-based binders were associated with reports of neurological and bone diseases. Members noted historical evidence that suggests such toxicity may have primarily been caused by exposure to aluminium in dialysis fluid sourced from municipal water supplies, and considered that this issue no longer applied to the New Zealand setting. The Committee noted that aluminium-based binders are used in Australia, Germany, Spain, and Italy (Mudge BMC Nephrology 2011, 12:20).
- 9.7 The Committee noted that there are a number of observational studies in humans with end stage CKD that show an association between elevations in serum calcium, phosphate and calcium phosphate with overall and cardiovascular mortality, for example in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (Tenori et al. Am J Kidney Dis 2008;52:519-530). The Committee accepted there was an unmet need for a different phosphate binder in patients with end stage renal disease.
- 9.8 The Committee noted that there were two trials provided by the applicant (Suki et al. Kidney Int 2007;72:1130-1137; Block et al. Kidney Int 2007;71:438-441). The

Committee also noted a separate meta-analysis of eight trials (Jamal et al. *Nephrol Dial Transplant* 2009;24(10):3168-3174).

- 9.9 The Committee noted the trial by Suki et al, also called the DCOR trial, compared all-cause mortality and cause-specific mortality in 2,103 haemodialysis patients randomised to calcium-based binders (calcium carbonate and calcium acetate) or sevelamer hydrochloride. The trial was open label, and the doses used or who chose them were not stated in the information provided. About 50% of patients in each group discontinued early, which was not satisfactorily explained. A non-statistically significant decrease in all-cause mortality was reported (15.0 vs. 1.61 per 100 patient years, HR 0.93 CI 0.79-1.1, $p=0.4$). No difference was shown in cardiovascular mortality, infection mortality, or other cause mortality. There was a non-statistically significant decrease in hospitalisations with sevelamer (median 1.0 vs. 1.3, $p=0.07$). The study authors note, as a post-hoc analysis, a separation of the survival curves after two years.
- 9.10 The Committee noted the trial by Block et al (the RIND trial), considered all-cause mortality and progression of the coronary artery calcium (CAC) score in 127 new to haemodialysis, randomized to sevelamer hydrochloride or an unstated calcium binder. After the first 18 months, patients were free to switch groups. The Committee noted that the paper does not state how many patients switched, and used a patient's original allocation when categorising for analysis. Mortality was 10.6/100 patient-years in the calcium group and 5.3/100 patient-years in the sevelamer group ($p=0.05$). After multivariate adjustment for age, race, sex, DBM, albumin, CRP, and baseline CAC, a statistically significant difference in mortality was reported (HR 3.1, 95% CI 1.23-7.61, $p=0.02$). The study observed that baseline CAC is a predictor of mortality.
- 9.11 The Committee noted the meta-analysis of Jamal et al. This study used standard searching techniques to find trials that compared calcium-based binders to non-calcium-based binders. Eight relevant trials were found, totalling 2,873 patients. There was a non-statistically significant reduction in all-cause mortality for sevelamer (relative risk of 0.68, 95% CI 0.41-1.11).
- 9.12 The Committee considered that the evidence for sevelamer was of poor quality and of mixed strength. Members doubted that mortality gains would be achieved and did not consider surrogate endpoints to be relevant to clinical gains. The Committee considered that any reduction in hypercalcaemia achieved by sevelamer instead of calcium was not borne out by improvements in hospitalisation rates. The Committee considered that the surrogate endpoints such as the coronary artery calcium score to be of little clinical importance without firm mortality data.
- 9.13 The Committee considered that there were safety issues surrounding the use of sevelamer hydrochloride. The Committee noted a study by De Santo et al (*J. Nephrol* 2006;19:S108-114) which was not provided by the supplier. This was a crossover study in which 16 patients spent 24 weeks on a calcium binder and 24 weeks on sevelamer. The study observed that patients receiving sevelamer hydrochloride developed low bicarbonate levels in both arms of the cross-over study, which resolved on switching to calcium. The study concluded that metabolic acidosis is a risk for patients receiving sevelamer hydrochloride. The study observed a statistically significant, but small, increase in calcium in the calcium binder group, but no episodes of hypercalcaemia were observed.

- 9.14 The Committee noted that sevelamer has been associated with cases of dysphagia, oesophageal tablet retention, bowel obstruction and perforation, and the sevelamer clinical studies excluded patients identified to be at risk of gastrointestinal adverse effects.
- 9.15 The Committee noted a website interview article that examined the two forms of sevelamer (carbonate and hydrochloride) and discussed theoretical reasons behind adverse effects caused by sevelamer hydrochloride (Medscape Nephrology, Jose Arruda 2008). The interview theorised that the chloride ions may be being exchanged for bicarbonate ions in the intestine. Members considered that PHARMAC staff should consider receiving an application for sevelamer carbonate, which may be associated with a lower risk of metabolic acidosis compared with the hydrochloride salt.

10 Renal multivitamin for patients with chronic kidney disease

Application

- 10.1 The Committee considered an application from Douglas Pharmaceuticals for funding a new composite renal multivitamin (Kidney Product) and mineral formulation for people on dialysis or with chronic kidney disease.

Recommendation

- 10.2 The Committee **recommended** that renal multivitamin be listed on the Pharmaceutical Schedule for patients with CKD who are on dialysis with a medium priority subject to the following Special Authority:

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

Either:

1. The patient has chronic kidney disease and is receiving either peritoneal or haemodialysis; or
2. The patient has chronic kidney disease grade 5 (CKD5), defined as patient with an eGFR of <15 ml/min/1.73m² BSA (body surface area)

- 10.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) the particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 10.4 The Committee considered the application for Kidney Product, which was supported by a panel of renal clinicians in New Zealand. The Committee noted that maintaining good nutritional status in patients with CKD is challenging, due to inadequate nutritional intake as a result of uraemic anorexia, nutritional restrictions and the unpalatability of the prescribed diet, co-morbidities such as diabetes requiring dietary restrictions, seasonal variation in access to fruit/vegetables. In addition, vitamins and minerals may be poorly absorbed or lost due to increased clearance in blood, excretion of protein-bound vitamins in patients with proteinuria, and losses of water-soluble vitamins may occur in the dialysate during dialysis.
- 10.5 The Committee noted that access to vitamin and mineral supplements appears to be variable in New Zealand. The application states that many CKD patients are purchasing preparations over-the-counter, which are potentially harmful for patients with renal problems because they do not contain the appropriate vitamin and mineral levels. The Committee also noted that CKD patients in low socioeconomic groups are less likely to self-fund supplements, and more likely to have inadequate nutrition, making them more susceptible to deficiencies. The Committee noted that adherence is often poor in patients with chronic kidney disease, especially as they are often on multiple medications in addition to nutritional supplements. The Committee noted that the prevalence of CKD is higher in Maori and Pacific peoples compared with the general population.
- 10.6 The Committee noted that the proposal identified several groups of patients who may potentially benefit from Kidney Product – those with CKD4 and CKD5, people on dialysis and renal transplant patients, in addition to a subgroup of CKD3 patients with malnourishment.
- 10.7 The Committee noted that no studies have been conducted for Kidney Product, and none were found for the comparable products available in the US and Australia. The evidence supplied in the application primarily looked at nutritional deficiencies and their effects in CKD patients. Three sets of guidelines were also considered from Kidney Disease Outcome Quality Initiative (KDOQI), Kidney Disease Improving Global Outcomes (KDIGO) and Caring for Australians with Renal Impairment (CARI).
- 10.8 The Committee noted the Dialysis Outcomes and Practice Study (DOPPS), a prospective longitudinal multicentre study of 16,345 adult haemodialysis patients reported by Vittorio et al. (Am J Kidney Dis 2004) and Fissell et al. (Am J Kidney Dis 2004;44:293-299). The study examined patterns of water-soluble vitamin use and evaluated mortality and hospitalisation as associated with vitamin use. Overall patient use of water-soluble vitamins ranged from 3.7% in the UK to 72% in USA. Large and significant variation was observed between countries, although use stable in each country throughout the study. In the USA, 100% supplements contained vitamin B6 and 12, and vitamin C, and 72% contained folate. The authors reported that patients taking water-soluble vitamins had a significantly lower mortality risk (relative risk (RR) 0.84; p 0.001) and although not significant, the risk for hospitalisation was also lower among patients taking vitamins (RR 0.94; p 0.24).
- 10.9 The Committee noted that several factors may contribute to the results of DOPPS, including: the effect of folic acid to reduce homocysteine levels and therefore possible reductions in cardiac mortality; that water-soluble vitamins may be associated with better nutritional intake, which has been shown to correlate with improved survival in

haemodialysis patients; and that vitamin use may be associated with more meticulous overall care at the dialysis units. The authors concluded that randomised controlled trials would be required to confirm the results of this study.

- 10.10 The Committee considered that vitamin D deficiency is common in CKD patients due to decreased exposure to sunlight, skin pigmentation (Maori and Pacific people have a higher risk of deficiency due to darker skin), loss of vitamin D-binding proteins due to proteinuria, reduced dietary intake, and impaired skin synthesis. The Committee considered that avoiding supplements containing vitamin A and E seemed reasonable in CKD patients.
- 10.11 The Committee noted a prospective controlled trial (Rucker et al. J Neph 2009;22:75) in 128 patients with stage 3 to 5 non-dialysis dependent CKD randomised 1:1 to receive 1000IU cholecalciferol or no intervention. After three months, the intervention group had a significantly higher mean 25-hydroxy-vitamin D level compared with the control group (26.8 vs 22.4ng/ml; $p < 0.0001$), adjusting for baseline levels. In terms of insufficiency ($< 30\text{ng/ml}$), oral cholecalciferol reduced the risk of insufficiency by 37% compared with a 2% increased risk in the non-treatment group. The authors commented on the fact that the optimal level of 25-hydroxy-vitamin D in CKD patients is unknown and some studies have shown that 25-hydroxy-vitamin D levels $> 40\text{ng/ml}$ are needed to reduce parathyroid hormone levels to normal. The Committee noted that this suggests that cholecalciferol levels higher than 1000IU/day may be needed.
- 10.12 The Committee considered a systematic review (Tonelli et al. BMC Medicine 2009;7:25 DOI:10.1186/1741-7015-7-25) assessing trace element status in haemodialysis patients. The authors identified 128 eligible studies that had measured blood/serum/plasma levels of at least one of a variety of trace elements, and calculated differences between dialysis patients and controls using differences in mean trace element level, divided by pooled standard deviation. The data suggested levels of selenium, zinc, and manganese were lower in haemodialysis patients compared with controls. The pooled standard mean differences exceeded 0.8 standard deviations.
- 10.13 The Committee noted that Kidney Product is a once daily capsule containing 14 ingredients, and that there is no such product available in the New Zealand market, but it is comparable with products available in the US and in Australia. The Committee noted that stability studies are currently underway and that these would need to be satisfactory prior to any decision to fund. The Committee noted that most, not all of the individual vitamins and minerals in the composite are available funded on the Pharmaceutical Schedule, but that five different tablets would need to be taken daily. The Committee noted that adherence to the once daily formulation is likely to be much greater.
- 10.14 The Committee noted that if Kidney Product was available, patients are also likely to be treated with vitamin D analogues, vitamin B12 injections, and may require additional iron supplementation.
- 10.15 The Committee noted that the cost of the multivitamin capsule is \$0.28 per day compared with the funded alternatives' \$0.26 total per day. The Committee noted that it is difficult to determine which products are being prescribed for this indication, and how many patients are buying products over the counter.

- 10.16 The Committee considered that the patient population most likely to benefit from Kidney Product are CKD patients on dialysis. The Committee considered that following renal transplantation, patients are likely to have a low need for supplementation due to improved renal function and did not recommend treatment for this group. The Committee considered that while the evidence for supplementation in patients with CKD was weak, it is reasonable to expect that patients on dialysis are at greatest risk of developing vitamin and mineral deficiencies.

11 Bortezomib for multiple myeloma

Application

- 11.1 The Committee reviewed an application from Janssen-Cilag for the widening of access to bortezomib on the Pharmaceutical Schedule for the re-treatment of patients with multiple myeloma who have relapsed after a good response (complete or partial response) to prior bortezomib treatment, including patients who had received prior bortezomib treatment in either the treatment naïve or relapsed/refractory setting.

Recommendation

- 11.2 The Committee deferred making a recommendation on bortezomib re-treatment for patients with multiple myeloma. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee (CaTSoP) for consideration.

Discussion

- 11.3 The Committee noted the results from the Mateos et al 2010 study (J Clin Oncol 28:2259-2266) which was a follow up of the VISTA study (San Miguel et al. NEJM 2008;359:906-917 and Dimopoulos et al (J Clin Oncol. 2009;27(36):6086-93). Members noted that 36 out of the 43 patients with multiple myeloma (MM) from the VMP (bortezomib, melphalan and prednisolone) arm in the Mateos et al study had bortezomib-based subsequent therapy. Median time to next treatment (TNT) was 28.1 months. The Committee noted that response rates to second-line bortezomib-, thalidomide-, and lenalidomide-based therapies were 41%, 37%, and 73%, respectively, after VMP, and 59%, 47%, and 67%, respectively, after MP; respective response rates to therapies received at third line and beyond were 47%, 53%, and 44% after VMP and 55%, 55%, and 43% after MP. The Committee considered that overall response rates (ORR) to bortezomib in the second line and third line/beyond settings were not very different, at 41% and 47% respectively in the VMP arm. In the group that received bortezomib in the second line setting, complete response rates were approximately 6% (in those with treatment free intervals (TFI) <12 months) and 14% (TFI >12 months).
- 11.4 The Committee noted the results of the REPRIEVE study in abstract form (Petrucci et al. Haematologica. 2010;95:152) which was an open-label, single arm prospective study involving 130 patients with MM (126 who were evaluable) who had received bortezomib retreatment after responding to bortezomib previously and had a treatment free period of ≥6 months. The Committee noted that patients had a median of 2 prior therapies. Patients received a median of 7 cycles of bortezomib retreatment and a maximum of 8 cycles. The Committee noted that the ORR was 39.7% and the depth of previous response was associated with the likelihood of repeat response to bortezomib

retreatment where those with previous history of CR had an ORR of 62.5% and those with a history of PR had an ORR of 52.1%.

- 11.5 Members considered the results of the EVEREST study (Sood et al. Am J Hematol 2009; 84(10):657-60) which was an open label prospective study involving 32 patients with progressive MM who had previously tolerated bortezomib with a minimum of PR for ≥ 4 months, received a median of 4 prior lines of treatment and went on to receive bortezomib retreatment. The Committee noted that patients received a median of 5 cycles (maximum 12 cycles) of bortezomib retreatment and ORR was 50%. The Committee also noted the results from the Bilalis et al study (Blood 2007; 110: abstract 4819) which showed an ORR of 50.1% in patients retreated with bortezomib. The Committee further noted that the 8 retrospective cohort studies provided in the application indicated similar effect sizes as the evidence above.
- 11.6 The Committee noted that overall, the strength and quality of evidence for bortezomib was weak for the comparison with thalidomide in this setting because there was no data from randomised studies. The Committee considered that the evidence indicates that bortezomib has the same/similar therapeutic effect as thalidomide in this setting. The Committee considered that if bortezomib is funded in this setting, it might replace some thalidomide usage, shifting thalidomide from second to third line treatment. Based on the Palumbo study (Palumbo et al. Hematology Journal 2004;5:318-324), there is an expectation of successfully shorter remissions with repeated lines of therapy where the average duration of thalidomide treatment fell from 17 (if thalidomide used after 1 line of chemotherapy) to 11 months (if thalidomide used after >1 lines of chemotherapy). The Committee considered that based on the assumptions above, this proposal would still not be cost-saving because the savings from reduced thalidomide drug cost (\$6700) is still less than withheld under S 9(2)(b) (ii) and S9 (2) (ba) of the OIA which would be the drug cost of extra bortezomib. The Committee also noted that the average duration of thalidomide treatment in New Zealand is 9 months.
- 11.7 The Committee considered that there are currently no problems with access to thalidomide in this setting. The Committee considered that there is no evidence to support the claim that bortezomib provides additional benefit over thalidomide; however, it might be a treatment option for patients unable to tolerate thalidomide treatment. The Committee also considered that the patient population most likely to benefit would be those with the best (most complete and durable) first-line response to bortezomib. This would not be readily apparent in patients who have undergone autologous peripheral blood stem cell transplants (APBSCTs).
- 11.8 The Committee also considered that there is no good evidence to support second and subsequent retreatments with bortezomib; however, if it is considered safe and inexpensive, multiple retreatments might continue until expected clinical benefit was negligible that is until disease is refractory or time to progression is less than 3 months.
- 11.9 The Committee considered that bortezomib would likely be dosed as per the REPRIEVE study (Petrucci et al. Haematologica. 2010;95:152), which is 1.0 or 1.3mg/m² on days 1, 4, 8 and 11 of 21-day cycles with patients likely to receive up to 8 cycles. The Committee considered that there is an unmet health need in this population because MM is currently an incurable illness. Members noted that there are generally worse outcomes for Maori with MM but the disparity is less pronounced than with other diseases.

- 11.10 The Committee considered that if bortezomib is funded for this patient population, it should be restricted to those who have had at least CR and PR during their initial treatment with bortezomib with ≥ 6 months TTP. The Committee considered it likely that if restricted this way, all patients who achieved CR or PR in their initial treatment with bortezomib would access retreatment, ranging between 38% and 71% (based on the APEX (Richardson et al. N Engl J Med 2005;352:2487-98) (and VISTA (San Miguel et al. NEJM 2008;359:906-917) trial results respectively).
- 11.11 The Committee considered that it would be appropriate to refer this application to CaTSoP, including for advice regarding what proportion of patients would receive bortezomib retreatment subcutaneously (instead of intravenously) and how many times bortezomib retreatment would be used.

12 Everolimus for sub-ependymal giant cell astrocytomas not amenable to neurosurgical resection

Application

- 12.1 The Committee reviewed an application from a group of clinicians for the funding of everolimus for progressively enlarging sub-ependymal giant cell astrocytomas (SEGAs) not amenable to neurosurgical resection.

Recommendation

- 12.2 The Committee **recommended** that everolimus be funded with high priority for short term (6 months) treatment prior to neurosurgery in patients with SEGAs.
- 12.3 The Committee also **recommended** that everolimus be funded with low priority for patients with SEGAs not amenable to neurosurgical resection.
- 12.4 The Committee recommended that the application for everolimus in SEGAs be referred to the Cancer Treatments Subcommittee (CaTSoP) for consideration and advice regarding possible Special Authority criteria.
- 12.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 12.6 The Committee noted that SEGAs occur in a proportion of patients with tuberous sclerosis complex (TS) and they are typically slow growing, commonly located near the intraventricular foramen connecting the lateral ventricles to the third ventricles. The Committee noted that the majority of SEGAs remain asymptomatic; however, a proportion do block cerebrospinal fluid (CSF) drainage leading to hydrocephalus, the consequences which are headaches, vomiting, visual disturbances, seizures,

developmental delay and death. Members considered that symptomatic SEGAs tend to occur in the second decade of life.

- 12.7 TS has a birth incidence of about 1 in 6000 ([Osborne et al. Ann NY Acad Sci. 1991;615:125-7), , and the proportion of TS patients with SEGAs range between 8% and 27% with 6%-9% of SEGAs being symptomatic. The Committee noted that in New Zealand neurosurgery is the treatment of choice for symptomatic SEGAs although it is associated with significant morbidity. Members noted that in the last 24 months there have only been 3 surgical resections in New Zealand, one being a partial resection and another receiving everolimus prior to surgery for complete resection. The Committee noted that one child with surgically refractory SEGA was recently commenced on everolimus. The Committee considered that these patient numbers were in line with the Sun et al study (Curr Med Res Op 2012;28(4):651-656) which identified 10,216 patients with TS claims, 421 of whom had SEGAs (4.1%) and 117 undergoing SEGA surgery (1.1%).
- 12.8 The Committee considered that most patients with TS have genetic mutations which result in the activation of mammalian target of rapamycin complex 1 (mTORC1), the inhibition of which is the mode of action of everolimus. The Committee noted the results from the EXIST-1 study (Franz DN et al. Lancet 2012; published online Nov 14. [http://dx.doi.org/10.1016/S0140-6736\(12\)61134-9](http://dx.doi.org/10.1016/S0140-6736(12)61134-9)) which was a double blind randomised controlled trial (RCT) comparing everolimus and placebo in 117 patients. The inclusion criteria for the study included one TS associated SEGA of at least 1cm and at least one of the following: (1) serial worsening (defined as an increase of at least 25% in volume of SEGAs) (2) presence of a new lesion 1 cm or greater in diameter; or (3) new or worsening hydrocephalus. Patients also had to be medically stable, unlikely to require surgery and not have critical hydrocephalus or imminent herniation.
- 12.9 The Committee noted that the median age of patients included in the study was 9.5 years with a median body surface area (BSA) of about 1m². The Committee noted that 27 (35%) of the everolimus patients achieved the primary endpoint of reduction in tumour volume by 50% or more from baseline (in the absence of new lesions or worsening) versus none in the placebo group in the ITT analysis (difference of 35%, 95% CI 15-52, p<0.0001). The Committee noted that only 34% of participants had a seizure present on baseline EEG with no change from baseline between groups overall or in the subset of those with seizures although groups were imbalanced at baseline).
- 12.10 The Committee noted that most adverse events were grade 1 or 2. Mouth ulceration occurred in 32% of everolimus participants versus 5% of placebo participants. Within the everolimus group there was one case of grade 1 herpes zoster, one case of grade 4 gastroenteritis and one case of grade 2 interstitial pneumonitis. The Committee noted that 49% of the everolimus participants versus 10% of the placebo participants required a dose reduction or temporary interruption of treatment due to adverse events. No adverse events lead to discontinuation of treatment. The Committee considered that the patients included in this study had less severe disease at enrolment compared with those proposed in the application.
- 12.11 The Committee noted the results from the Krueger et al study (N Engl J Med 2010;363:1801-11), which was a prospective, open label, single arm study that included 28 patients. Members noted that eligible patients were 3 years of age or older, with serial growth of SEGA and medically stable. The median age of participants was

11 years and only 4 had previously undergone partial resection whilst 6 had hydrocephalus. The Committee noted that there was a reduction of mean and median tumour volume at 6 months (primary outcome), 1.15 and 0.83cm³ respectively (p<0.001) with 9 (32%) of patients achieving a 50% reduction in SEGA volume. The effect appeared to persist to 18 months and no patients developed new lesions. One patient had an 18% reduction in SEGA volume at 6 months but a 16% increase when compared with baseline at 18 months. The Committee considered that the evidence for reduction in seizure frequency in this study was inconclusive.

- 12.12 The Committee noted that adverse events were reported in all patients where most were grade 1 and 2. Stomatitis, upper respiratory tract infections and pyrexia were common and two participants had grade 3 infections (bronchitis and pneumonia). Longer term data on this study is available in poster form (Krueger et al 2011, presented at 2011 Summit on Drug Discovery in TSC and Related Disorders, Washington DC) which reported median duration of exposure of 34.2 months (range 4.7-47.1 months). Reduction in volume appeared to continue with time, with data from the 24 participants at 24 months reporting that 50% had achieved a ≥50% volume reduction from baseline and 79.2% achieving a ≥30% reduction. The Committee noted that 3 (12%) of participants had progression of volume from baseline ≥25% and treatment was continued in these participants, with reduction (not quantified) subsequently reported in 2 of the 3 participants. This study showed a similar adverse event profile with no evidence of escalation with prolonged treatment. Again, the Committee considered that this study included patients with less severe disease.
- 12.13 The Committee noted that overall the strength and quality of evidence is moderate from one small, good quality RCT and one small open label study which showed that everolimus has a clinically relevant effect in SEGA reduction but the studies may be less relevant to the population presented in the application. However, the Committee considered that it would not be unreasonable to assume that everolimus would benefit the SEGA population in the application.
- 12.14 The Committee considered that neurosurgery is associated with significant risk/complications. Compared with the six months preceding surgery, the post-surgery prevalence rates increased by 23-26% for seizures, 21-26% for hydrocephalus, 17-19% for headaches and 6-9% for stroke or hemiparesis (all p<0.05) (Sun et al. Curr Med Res Op 2012;28(4):651-656).
- 12.15 The Committee considered that everolimus does not have the same or similar effect to any currently listed pharmaceuticals, but noted that sirolimus in theory may have similar effect in this patient population, due to a class effect. The Committee considered that if everolimus is restricted to those with inoperable SEGAs, the appropriate comparator would be no surgical resections. However, the complications of no surgical resection include hydrocephalus for which neurosurgical placement of a ventriculo-peritoneal (VP) shunt is likely to occur. VP shunts are associated with neurosurgical and post-surgical costs and complications (obstruction, infection and post-shunt headache) and anaesthesia-related risks.
- 12.16 The Committee considered that if everolimus is used prior to neurosurgery, it will likely be for one course only and tumour shrinkage would likely improve surgical outcome, even increasing the rates of complete resection. The Committee considered it unlikely that radical tumour removal would be more likely in previously inoperative SEGAs as a

result of everolimus treatment, but it would likely lead to reduced risk of symptomatic disease progression. The Committee noted there is currently no difficulty with access to elective neurosurgery but access to emergency neurosurgery for complications related to shunt blockage for example could be a problem due to long distances from tertiary centres for many patients with delays resulting in potential morbidity. If everolimus were to be funded, it would not be likely to increase the number of neurosurgeries but conversely could potentially reduce numbers as it would prevent surgeries otherwise undertaken despite the high risk because of the lack of alternative treatments available.

- 12.17 The Committee considered that the patient populations most likely to benefit from everolimus would be 1. those patients with symptomatic SEGAs not amenable to surgery and 2. those with symptomatic SEGAs prior to surgery where there is expected to be considerable benefit obtained with surgery (6 months treatment). The Committee considered that there is no evidence to suggest this condition is more prevalent in Maori or Pacific peoples. The Committee considered that if everolimus were to be funded for the populations outlined above, up to one patient/year would access it under the inoperable criteria and up to one patient/year for the pre-surgical criteria.

13 Carbetocin in uterine atony and excessive bleeding following elective caesarean section

Application

- 13.1 The Committee considered an application from Pharmaco (NZ) Ltd to fund carbetocin (Duratocin) for the prevention of uterine atony and excessive bleeding following elective caesarean section.

Recommendation

- 13.2 The Committee **recommended** that carbetocin only be listed if cost neutral to the administration of oxytocin.
- 13.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 13.4 The Committee noted postpartum haemorrhage (PPH), defined as blood loss of more than 500 ml during the first 24 hours after childbirth, is a major cause of morbidity and mortality. The Committee also noted that carbetocin is a synthetic oxytocin analogue with reduced potency and prolonged activity on uterine smooth muscle. Carbetocin is indicated for the prevention of uterine atony and PPH following elective caesarean section and has not been studied in high risk PPH, multiparous pregnancy or prolonged labour.

- 13.5 The Committee considered the evidence provided by the supplier. There were four key studies comparing oxytocin and carbetocin in women undergoing caesarean sections: Dansereau et al (Am J Obstet Gynaecol 1999;180(3 Pt 1):670-6), a double blind, randomised clinical trial comparing carbetocin vs. oxytocin in prevention of uterine atony after elective caesarean section; Attilakos et al (BJOG 2010;117:929-936), a double blind randomised controlled trial (RCT) comparing carbetocin vs. oxytocin for the prevention of PPH following elective or emergency caesarean section; Boucher et al (J Peritonology 1998;18(3):202-7), an RCT comparing the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone in patients undergoing elective caesarean section; and Borruto et al (Arch Gynecol Obstet 2009;280(5):707-712), an RCT studying the utilization of carbetocin for the prevention of PPH after elective or emergency caesarean section. The Committee also noted a Cochrane Review by Su et al (Cochrane Review July 2007, Issue 3) reviewing oxytocin agonists for preventing PPH.
- 13.6 The Committee noted that 635 patients completed the Dansereau study; 317 in the carbetocin arm who received a 100 mcg bolus of carbetocin followed by a placebo infusion, and 318 in the oxytocin arm who received a 5 IU bolus followed by 20 IU infusion over 8 hours following delivery. The primary outcome was the need for additional oxytocic drugs within 48 hours of delivery. The Committee noted that after correction for the imbalance of gestational diabetes patient between the two groups, the carbetocin group required additional oxytocic intervention (4.7% versus 10.1%, $p < 0.05$). Differences in the secondary outcomes between the two groups were the median time for intervention (2 hours with carbetocin vs. 11 minutes with oxytocin) and uterine massage (2.8% with carbetocin vs. 7.5% with oxytocin). The Committee noted that combinations of these two outcomes were statistically different while there were no significant differences in the other secondary outcomes - uterine tone, fundal position, haemoglobin drop, platelet count, blood chemistry.
- 13.7 The Committee noted that in the Attilakos study, 189 patients were randomised to 5IU carbetocin and 188 to 100 mcg oxytocin administered as a slow IV infusion over 30-60 seconds. The primary outcome was the proportion of women that needed additional oxytocic interventions. In the oxytocin arm 45.5% of women required additional oxytocic vs. 33.5% in the carbetocin arm (relative risk (RR) 0.74, 95% CI 0.57–0.95). There were no significant differences in the secondary outcomes including major PPH, blood transfusions and fall in haemoglobin.
- 13.8 The Committee noted that the Boucher study compared the effects of oxytocin vs. carbetocin on intraoperative blood loss and uterine atony following caesarean section. In the oxytocin group, 28 patients received 2.5 IU iv oxytocin followed by 10 IU rapid infusion and 20IU over 16 hours while the 29 in the carbetocin group received 100 mcg carbetocin followed by matching placebo. Subset analysis (which excluded two patients who received oxytocic intervention in the operating room and one extreme outlier) revealed that 79% of patients in the carbetocin group sustained blood loss of < 200 ml compared to 53% in the oxytocin group ($p = 0.04$). More patients in the carbetocin group had uterine fundus below umbilicus than in the oxytocin group at the end of the recovery room period (64% versus 39%).
- 13.9 The Committee noted that Borruto et al studied women with at least one risk factor for PPH undergoing elective or emergency caesarean section. In the carbetocin group, 52 patients received 100 mcg of carbetocin and in the comparative group 52 patients

received 10IU of oxytocin by infusion over two hours. The primary outcome measure was the proportion of women requiring additional oxytocic intervention for uterine atony. In the carbetocin group, 3.8% required additional medication vs. 9.6% in the oxytocin group ($p<0.01$) and 38.4% of those in the carbetocin group required uterine massage vs. 57.7% in the oxytocin group ($p<0.01$).

- 13.10 The Committee noted the Cochrane Review gave a balanced account of all published papers and had concluded that there was no difference in PPH between carbetocin and oxytocin. The Cochrane review also concluded that there was no difference in blood transfusions, blood loss or haemoglobin and haematocrit levels. The Committee noted that with regard to uterogenic effects there was a reduction in the use of uterogenic agents in the carbetocin groups (RR of 0.62 95% CI 0.44–0.88). There was no difference in adverse events noted between the two agents.
- 13.11 The Committee noted an audit had been carried out at National Women's Health, Auckland, where 50 women having elective caesarean sections received 100 mcg IV carbetocin immediately after delivery of the baby and before placental delivery. Follow up data was available for 45 of the women, of whom 14% had uterine fundus above the umbilicus, 16% had unsatisfactory uterine tone, 22% needed additional uterogenics and over 40% had PPH. Of those with PPH, 17 patients' blood loss was between 500-1,000 ml and 4 patients lost between 1000 to 1500ml. In the supporting information, National Women's Hospital suggested that carbetocin is a useful agent for reducing the high incidence of PPH. The Committee considered that evidence does not support this assumption and factors such as the selection of (higher risk) patients may have contributed to the high incidence of PPH at that hospital.
- 13.12 The Committee noted that a survey by Mocker et al (ANZJOG 2010;50:30-35) of practicing obstetricians in New Zealand and Australia reported that 98% administered oxytocin bolus at the time of caesarean section (mostly 5IU in New Zealand). An additional infusion was administered routinely by 53% of respondents and electively by 44%. The most common infusion dose was 40IU administered over four hours, but there were up to 68 different variations of the infusion regimen used.
- 13.13 The Committee noted that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommend the use of oxytocin for the prevention of PPH. The Committee also noted that carbetocin was not included in the UK Guidelines due to the cost. The Committee further noted that the Society of Obstetricians and Gynaecologists of Canada recommends carbetocin over oxytocin to prevent PPH and decrease the need for consequent therapeutic interventions.
- 13.14 The Committee noted that carbetocin is being used in three hospitals in New Zealand and that an application for use in National Women's Health had been made and was included in the supplier's application. The Committee also noted that carbetocin uptake has not increased during the last few years in DHB hospitals.
- 13.15 The Committee considered, if funded, carbetocin is likely to be used for active management of 3rd stage of labour followed by caesarean section outside the registered indications. There is also potential for its use after active management of labour following a vaginal delivery.

- 13.16 In summary the Committee noted that carbetocin has a prolonged action and is a useful uterotonic for active management of 3rd stage of labour. Patients seem to require less uterotonics and iv infusions. The Committee considered that there is little evidence that carbetocin is superior to oxytocin in preventing PPH.
- 13.17 The Committee noted that the cost difference is significant and recommended that carbetocin be listed in the Pharmaceutical schedule only if cost neutral to administration of oxytocin.