

PTAC meeting held 10 & 11 May 2012

(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.

Contents

1	Record of PTAC meeting held February 2012	3
2	Subcommittee Minutes	3
3	Natalizumab for Multiple Sclerosis	5
4	Widening Access of Temozolomide for Oligodendroglial Tumours	9
5	Mycophenolate	11
6	Gemcitabine for Metastatic Breast Cancer	13
7	Capsaicin Topical Cream for Osteoarthritis	15
8	Denosumab for Postmenopausal Osteoporosis	17
9	Testosterone Undecanoate	20
10	Azithromycin for Pertussis, Neonatal Conjunctivitis and Pneumonia	22
11	Sildenafil for Raynaud's Phenomenon	26

1 Record of PTAC meeting held February 2012

1.1 The Committee reviewed the minutes of the PTAC meeting held on 16 and 17 February 2012 and made the following amendments:

1.1.1 Paragraph 7.5 change: “FEV₁/FEV <70%” to “FEV₁/FVC <70%”

1.1.2 Paragraph 9.1 change: “relapse remitting multiple sclerosis” to “relapsing remitting multiple sclerosis”

1.1.3 Paragraph 9.9 change: “MRI parameters were significantly improved when patients were receiving fingolimod” to “MRI parameters deteriorated significantly less when patients were receiving fingolimod”

1.1.4 Paragraph 13.5 change: “in whom splenectomy has been deemed inappropriate” to “in whom splenectomy has been deemed inappropriate or ineffective”

2 Subcommittee Minutes

2.1 Anti-Infective Subcommittee – 22 February 2012

2.1.1 The Committee noted and accepted the record of the meeting in relation to items Conflicts of Interest, Record of Previous Meetings (22/06/09, 08/04/2010 and 13/10/2010), Clinically Recommended Action Points and Therapeutic Group Review.

2.1.2 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.

2.2 Anti-Infective Subcommittee – 1 March 2012

2.2.1 The Committee noted and accepted the record of the meeting in relation to items Conflicts of Interest, Clinically Recommended Action Points, Matters Arising, Therapeutic Group Review, Posaconazole and Valganciclovir.

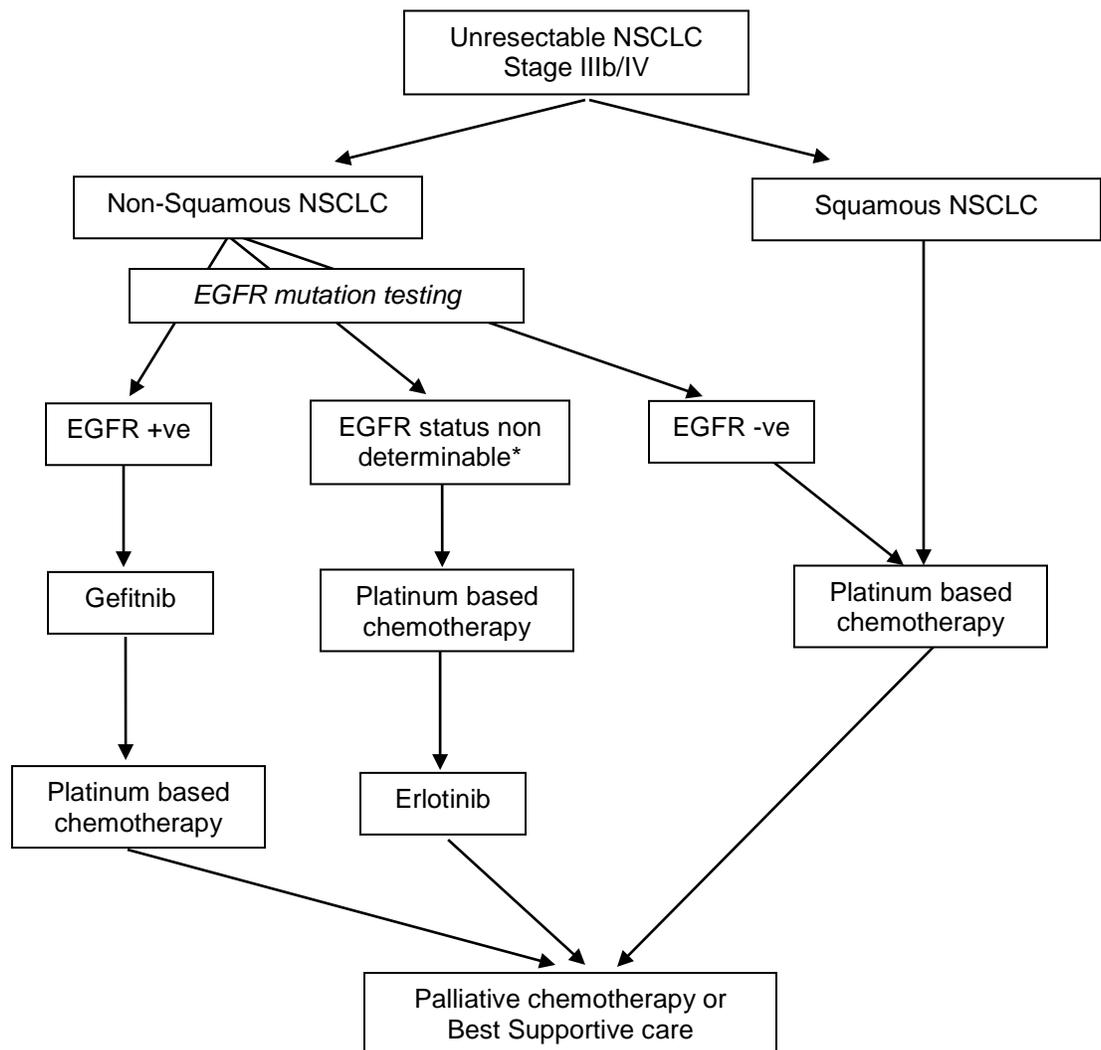
2.2.2 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee’s recommendations in relation to these items, and noted PTAC would be formally reviewing these items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

2.3 Cancer Treatments Subcommittee – 2 March 2012

2.3.1 The Committee noted and accepted the record of the meeting in relation to items Conflicts of Interest, Minutes of Previous Meeting (with the exception of item 2.2 discussed below), Matters Arising, Review of Cancer Treatment

Funding Applications, Therapeutic Group Review Including CaEC Review and Vemurafenib for Metastatic Melanoma Positive for BRAF V600 Mutation.

2.3.2 The Committee noted the changes to the NSCLC treatment algorithm the Subcommittee made to its 18 November 2011 minute (item 4.12). The Committee considered that there was some confusion regarding the treatment algorithm for squamous cell patients and **recommended** that the algorithm be split into 4 groups of patients for ease of reference; 1) Non-squamous EGFr positive, 2) non-squamous EGFr negative, 3) non-squamous EGFr non determinable and 4) squamous cell patients. Members recommended that the following patient treatment algorithm.



*result inconclusive or insufficient biopsy sample available

- 2.3.3 The Committee noted item 4, where the Cancer Treatments Subcommittee had reviewed the application from Roche Products NZ Ltd for the funding of vemurafenib (Zelboraf) for patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation. The Committee did not support the Cancer Treatments Subcommittee's recommendation and reiterated its February 2012 **recommendation** that the application be declined.
- 2.4 Diabetes Subcommittee Teleconference – 8 December 2011
- 2.4.1 The Committee noted and accepted the record of the meeting.
- 2.5 Ophthalmology Subcommittee – 9 March 2012
- 2.5.1 The Committee noted and accepted the record of the meeting in relation to items Conflicts of Interest, Previous Minutes, Clinically Recommended Action Points, Therapeutic Group Review and Preservative Free Eye Drops.
- 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 Natalizumab for Multiple Sclerosis

Application

- 3.1 The Committee considered an application to fund natalizumab (Tysabri) for the treatment of relapsing remitting multiple sclerosis (RRMS) from Biogen Idec.

Recommendation

- 3.2 The Committee deferred its recommendation pending further advice from the Neurological Subcommittee and MSTAC on both the current application for natalizumab and clinically optimal treatment algorithms (i.e. combinations of multiple sclerosis (MS) treatments, clinical eligibility, sequencing, etc.) for MS therapies in general. This is to inform further analysis by PHARMAC staff as to its cost-effectiveness, where currently such analysis is pending expert advice as to the most appropriate treatment algorithms to model.

Discussion

- 3.3 The Committee noted that natalizumab is a monoclonal antibody given by intravenous infusion every 4 weeks and therefore is a hospital treatment. The Committee also noted that natalizumab is believed to inhibit inflammatory cells crossing the blood brain barrier to exert its effect on RRMS.
- 3.4 The Committee considered the evidence provided in the form of two large (Pohlman et al. N Engl J Med 2006; 354: 899-910; Rudick et al. N Engl J Med 2006; 354:911-23) and two small randomised controlled trials (RCTs) (Miller et al. N.Engl J Med

2003;348:15-23; Goodman et al. Neurology 2009; 72: 806-12), partial outcome reporting from one large RCT (Miller et al. J Neurol 2007; 68: 1390-401), a sub-group analysis of the two large RCTs (Hutchinson et al. J Neurol 2009; 256:405-15), a Cochrane meta-analysis of the RCTs (Pucci et al. Cochrane Database of Systematic Reviews 2011;10:CD007621).

- 3.5 The Committee considered the randomised, double-blind parallel group study in which patients with RRMS or secondary progressive MS were randomised to receive either placebo (n=71) or natalizumab in 3 mg/kg (n=68) or 6 mg/kg (n=74) doses every 4 weeks for six months (Miller et al. N.Engl J Med 2003;348:15-23). The Committee noted that the primary outcome was the number of new MRI enhancing lesions and secondary outcomes included relapse frequency. The Committee noted that the patient population in this study was likely to have more advanced disease compared with New Zealand patients. The Committee noted that the combined relative risk for relapse for the natalizumab vs. placebo was 0.48 (95% confidence interval (CI) 0.22 to 1.04; p=0.067) and noted that there were fewer new MRI lesions in the natalizumab groups (1.1) compared with. placebo (9.6); however no confidence intervals were reported for this outcome variable.
- 3.6 The Committee considered the AFFIRM study (Pohlman et al. N Engl J Med 2006;354:899-910), a double-blind, parallel group study involving 942 patients with RRMS randomised (2:1) to receive either 300 mg natalizumab or placebo intravenously every four weeks for more than 2 years. The primary outcomes were the relapse rate measured after one year and sustained disability, measured by the EDSS at two years. The Committee noted that relapses were reported as 0.78 at one year for the placebo arm and 0.27 for the natalizumab group. The Committee considered that, following analysis, the relative risk of annual relapse rates for natalizumab vs placebo was 0.5 (95% CI 0.39 to 0.64, p<0.001). The Committee noted that no mean values were reported for EDSS outcomes, however Kaplan Meyer estimates of progression at two years were 29% for the placebo group and 17% for the natalizumab group. The Committee noted that there were no reported cases of progressive multifocal leukoencephalopathy (PML), however 4% of patients had an allergic reaction to the infusion.
- 3.7 The Committee considered a double-blind parallel group study (SENTINEL) with 1171 patients who, despite previous interferon beta-1-alpha (beta-IF) therapy had had at least one relapse during the previous 12 month period (Rudick et al. N Engl J Med 2006;354:911-23) Participants were randomised to receive 300 mg natalizumab (n=589) or placebo (n=582) intravenously every 4 weeks for up to 116 weeks in addition to continued IF therapy. The Committee noted that the relapses after one year were 0.81 in the placebo arm and 0.38 in the natalizumab group, and Members inferred from these data a relative risk of relapse for natalizumab vs placebo at one year to be 0.57 (0.47 to 0.68, p<0.001). The Committee noted the Kaplan-Meier estimates of the cumulative probability of progression at two years were 23% with natalizumab and 29% for the placebo arm. The Committee noted that there were two cases of PML reported, and that antibodies to natalizumab developed in 11.9% of patients.
- 3.8 The Committee considered a Cochrane review (Pucci et al. Cochrane Database of Systematic Reviews 2011;10:CD007621) reported that the pooled risk of at least one

relapse at two years natalizumab vs control was 0.57 (0.47 to 0.69) and the proportion with progression at two years of natalizumab vs. control was 0.74 (0.62 to 0.89).

- 3.9 The Committee considered 14 cohort and registry studies also provided in the application: Oturai et al. Eur J Neurol 2009; Outteryck et al. J Neurol 2009; Putzki et al. Eur J Neurol 2009; Prosperini et al. Neurol Sci 2010, Putzki et al. Eur Neurol 2010; Putzki et al. Eur J Neurol 2010; Sangalli et al Neurol Sci 2010; Belachew et al. Eur J Neurol 2010; Krysko et al. Can J Neurol Sci 2011; Mancardi et al. Neurol Sci 2011; Melin et al. Ann Neurol 2011; Prosperini et al. MSJ 2011; Castillo-Trivino et al. PLoS One 2011; Horga et al. Rev Neurol 2011. The Committee considered that for the 11 studies that reported a before-and-after annualised relapse rate (ARR), the median rate ratio for ARRs (comparing ARRs following natalizumab treatment with baseline ARRs before treatment) was 0.16, which the Committee considered contrasted appreciably with the median rate ratio for ARRs in the three RCTs (comparing natalizumab treatment group ARRs with standard care control group ARRs) of 0.46. The Committee noted that the median incidence of antibody formation from 11 of the studies was 4.5% and the median incidence of allergy/infusion reactions from all 14 studies was 4%.
- 3.10 The Committee considered that the evidence provided was a mixture of Scottish Intercollegiate Guidelines Network (SIGN) level 1+ grade evidence, being from well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias, together with many SIGN level 3 studies (non-analytic uncontrolled observational studies) with a high risk of bias. The Committee considered that, in summary the evidence suggests that compared with controls, natalizumab reduces relapse rates and lowers disability progression more effectively than placebo to 2 years. The Committee considered that natalizumab is likely to have a similar therapeutic effect to fingolimod.
- 3.11 The Committee considered that the indirect analyses provided by the supplier suggest that natalizumab may be more effective than beta-interferon and glatiramer, but not fingolimod in reducing annual relapse rates and two year relapse rates, but no different for EDSS than beta-interferon and glatiramer and more effective than fingolimod. The Committee considered that in the absence of direct comparator trials, these conclusions are tentative and suggest that for disability progression there is no evidence of a difference.
- 3.12 The Committee considered that there is some evidence that a combination of natalizumab and glatiramer or beta-interferon would be superior to monotherapy with either agent. The Committee considered that the majority of the cohort studies are mainly in patients with unsatisfactory responses to first line therapy, providing some weak evidence that natalizumab could replace those on currently funded therapy in New Zealand who meet the stopping criteria. Overall, the Committee considered that switching treatments rather than using dual therapy would result in a lower risk of adverse effects.
- 3.13 The Committee considered a recent review of natalizumab safety and monitoring reported by Kappos et al. (Lancet Neuro 2011;10:745-58) which was additional to the suppliers submission. The authors reported that natalizumab is associated with rare but serious adverse events including hepatic injury, possibly lymphoma and melanoma and herpes viral infections including herpes encephalitis. The Committee considered

that the most concerning adverse effect is PML, the incidence of which is between 1 per 1000 patients or up to 4.3 per 1000 patients for patients who receive more than 24 infusions or two years treatment. The Committee considered that testing for JC virus prior to starting therapy may predict those more likely to develop PML, although the exact role of such testing in clinical practice is yet to be determined. The Committee considered that the costs of natalizumab administration and monitoring is likely to increase health sector expenditure in comparison to other funded treatment, and there would be a very high level of treatment burden for any patient who developed PML.

- 3.14 The Committee considered the subgroup analyses of data from the AFFIRM and SENTINEL studies, reported by Hutchison et al (J Neurol 2009;256:405-415). The Committee noted that the results are published as separate hazard ratios for progression for multiple sub-groups, some with multiple levels. The Committee considered that as there is no evidence that any statistical tests for interaction were undertaken, it is difficult to infer the difference in the hazard of progression in any subgroup. The Committee considered that there was insufficient information presented in the paper for calculating a possible interaction term.
- 3.15 The Committee considered that, in the absence of statistical evidence that the effect in subgroups differs from the overall effect of the treatments, the pooled effects from meta-analysis or, where appropriate, the effect of all groups combined should be used in cost utility analyses when comparing natalizumab with other treatments. The Committee noted a lack of statistically robust evidence to indicate that the post hoc 'highly active subgroup' of patients in the AFFIRM trial (Hutchinson et al 2009) differed significantly from the overall intention-to-treat population in the AFFIRM trial (Poleman et al 2006). The Committee therefore considered that the Cochrane pooled risk for disease progression was an appropriate basis for modelling, which calculated the proportion with disease progression at two years of natalizumab therapy compared with control at 0.74 (95% CI 0.62 to 0.89).
- 3.16 The Committee recommended that further advice be sought on future treatment algorithms for MS treatments considering the recent funding application for fingolimod and the recommendation to amend the entry criteria for currently funded treatments. The Committee noted that while it does not consider beta-interferon and glatiramer to be particularly effective treatments, there is a longer experience with these agents and their adverse event profiles in a New Zealand population. The Committee considered that it appears that natalizumab and fingolimod have similar efficacy but less international experience, and both have different adverse event profiles which may not be fully established in real clinical populations.
- 3.17 The Committee considered that a number of treatment scenarios should be assessed, including beta-interferon and glatiramer as first line therapies with switching to either or both fingolimod or natalizumab as second line, with consideration given to those patients who have met the current stopping criteria who might now be considered for a trial of fingolimod or natalizumab. The Committee considered that stopping criteria should be consistent across all therapies.
- 3.18 Given the risks of long term use and perceived benefit of short term use in preventing relapses, some members considered that natalizumab could prove to be the most clinically optimal agent for use early in disease before other agents, but these views were contingent on further advice (see paragraph 8.19 following).

- 3.19 The Committee indicated that clear clinical guidance on the clinically most appropriate treatment algorithms was needed to guide assessment of cost effectiveness.
- 3.20 The Committee considered that should natalizumab be funded, the clinical risk due to the lack of long term safety and efficacy data and the high fiscal risk, treatment should be administered using a process similar to that with current funded multiple sclerosis treatments through MSTAC.

4 Widening Access of Temozolomide for Oligodendroglial Tumours

Application

- 4.1 The Committee considered an application from a clinician, supported by a number of medical and radiation Oncologists, requesting funded access to temozolomide be widened to include all patients with newly diagnosed grade 3 primary brain tumours including anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA).

Recommendation

- 4.2 The Committee **recommended** that the application be declined.
- 4.3 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, (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

- 4.4 The Committee noted that temozolomide was currently funded for patients with newly diagnosed anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM). Members noted that brain tumours often have mixed histology, with some astrocytic and/or oligodendroglial cell line components, therefore, histology results of biopsy may not always accurately reflect tumour cell pathology.
- 4.5 The Committee noted that the current funding criteria for temozolomide did not specify a 'histological diagnosis' of GBM or AA, thus if a clinician genuinely considered that a patient's tumour was behaving as a GBM or AA, and that the available histology was a false-negative diagnosis due to non-specific tissue sampling, they would be able to access funding without the requirement for further biopsy.
- 4.6 The Committee noted that the applicant considered that funding of temozolomide should include all grade 3 tumours (anaplastic oligodendroglioma (OA), anaplastic oligoastrocytoma (AOA) as well as currently funded anaplastic astrocytoma (AA)).

- 4.7 The Committee noted that since the emergence of molecular genetics and the establishment of co-deletion in chromosomal arms 1p and 19q (del1p19q) as a "genetic signature" of oligodendroglioma fewer patients were being diagnosed with AA.
- 4.8 The Committee considered that grade 3 gliomas are not curable; with treatment aimed at reducing symptoms and prolonging disease free progression and survival times. Members noted that standard treatment comprises debulking surgery where possible combined with adjuvant radiation and chemotherapy, usually PCV oral procarbazine, combined with infusional lomustine (CCNU) and vincristine (PCV).
- 4.9 The Committee considered evidence from a large number of studies, mainly single arm phase II and retrospective clinical trials of chemotherapy treatment, mainly PCV in patients with various high grade brain tumours. Members considered that overall the strength and quality of the evidence was weak for the decision question posed regarding health gains of temozolomide compared with PCV in patients with newly diagnosed AO and AOA.
- 4.10 The Committee noted that the largest of the studies retrospectively examined the outcome of 1013 patients with newly diagnosed anaplastic oligodendroglioma or anaplastic astrocytoma treated surgically followed with radiation alone (RT n=200) or chemotherapy (PCV or temozolomide) in combination with radiation (CT+RT n=528) or chemotherapy alone CT (n=201) between 1981-2007 (Lassman et al Neuro Oncology 13 (6):649-659, 2011). Members noted that overall survival (OS) and time to progression was longer in the CT+RT treated patients (median OS 7.3 years).
- 4.11 The Committee noted that an analysis of response by chemotherapy type (PCV vs temozolomide) was undertaken in patients with 1p19q codeleted tumours. PCV significantly improved median time to progression (TTP) compared with temozolomide (PCV 7.6 years, TMZ 3.3 years, $p=0.0186$) and, although not statistically significant, there was a trend towards better OS with PCV compared with temozolomide (PCV 10.5 years, TMZ 7.2 years, $p=0.16$). Members noted that the study was underpowered for direct comparison between PCV and temozolomide, however, members considered that whilst no firm conclusion could be made it appeared that temozolomide was not as efficacious as PCV in patients with 1p19q codeleted tumours.
- 4.12 The Subcommittee considered that evidence from a Phase III study (RTOG 9402, Cairncross et al, J Clin Oncol 24(18) 2006:2707-2714) comparing PCV followed by RT versus RT alone in 289 patients with newly diagnosed AO and AOA demonstrated patients with 1p19q codeleted tumours had significantly longer median overall survival (>7 yrs vs 2.8 yrs, $p<0.001$) and a significantly lower risk of tumour progression.
- 4.13 The Committee considered that whilst there was some evidence of increased toxicity, particularly nausea, with PCV compared with temozolomide, the evidence was weak and in some cases likely to have pre-dated modern antiemetic protocols.
- 4.14 The Committee considered that overall temozolomide was easier to administer than PCV and there was weak evidence to suggest that it had a better toxicity profile. However, members noted that temozolomide was more expensive than PCV and considered that overall the evidence demonstrated that PCV may be more efficacious than temozolomide in oligodendroglioma, particularly in patients with 1p19q codeleted tumours.

- 4.15 The Committee considered that testing for 1p19q codeletion should be encouraged and that in these patients PCV should be offered as first line treatment.

5 Mycophenolate

Application

- 5.1 The Committee reconsidered an application from PHARMAC staff, prompted by e-mail correspondence from a clinician, for the funding of mycophenolate mofetil (MMF) on the Pharmaceutical Schedule to be widened to include induction and maintenance treatment of patients with lupus nephritis (LN) or vasculitis.

Recommendation

- 5.2 The Committee **recommended** that mycophenolate be funded for induction and maintenance treatment of patients with lupus nephritis or vasculitis under Special Authority criteria as recommended by the Rheumatology Subcommittee of PTAC at its October 2011 meeting. Members gave this recommendation a high priority.
- 5.3 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

- 5.4 The Committee noted that at its May 2011 meeting it recommended that mycophenolate mofetil (MMF) be funded for a maximum of 24 weeks' induction treatment in patients with LN (with a high priority) or vasculitis (with a low priority) who have not responded to cyclophosphamide or in whom cyclophosphamide use is not tolerated or is contraindicated and that the application for funding of MMF for maintenance treatment in LN or vasculitis be declined.
- 5.5 The Committee noted that at its October 2011 meeting the Rheumatology Subcommittee of PTAC agreed with PTAC's recommendations regarding induction treatment but considered that there would be a proportion of patients who receive MMF induction treatment followed by azathioprine maintenance who then relapse. Members noted that the Subcommittee considered that MMF re-induction and maintenance treatment should be an option for these patients, noting that this was a different patient group from that considered by PTAC for MMF maintenance treatment. Members noted that following review of the Subcommittee's recommendations it was concerned that there was insufficient evidence for MMF re-induction following azathioprine failure and requested that PHARMAC staff resubmit the application for its review.
- 5.6 The Committee noted 2 new papers that had been published since its previous review. The first was the maintenance phase of the ALMS study which was a 2-phase

(induction and maintenance) randomised controlled study, comparing MMF with intravenous (IV) cyclophosphamide (both in combination with prednisone) in patients with LN (Dooley et al N Engl J Med 2011;365:1886-1895). Members noted that it had previously reviewed the outcomes of the extension phase of this study in abstract form (Ginzler et al 2010). Members noted that the publication confirmed the previous abstract findings. Members noted that in the maintenance study 227 patients who responded to induction treatment (MMF or cyclophosphamide) were then randomised to receive MMF (2 g/day) or azathioprine (2mg/kg/day) maintenance treatment. Members noted that MMF was superior to azathioprine in terms of the primary endpoint, which was a composite of time to treatment failure.

- 5.7 The Committee noted a second new publication of longer term follow up of the previous reviewed Grootscholten study, comparing induction with azathioprine or cyclophosphamide, followed by azathioprine maintenance therapy, in 87 patients with proliferative LN (Arends Annals of Rheumatic Disease 2011). Members noted that this evidence demonstrated that after a median follow-up of 9.6 years there was no difference between the two patient groups in terms of sustained doubling of serum creatinine, end stage renal disease or mortality, however, more renal relapses occurred in patients who had received azathioprine induction. Based on this study the Committee noted that azathioprine could be a potential alternative treatment for treatment induction in lupus nephritis. The Committee also previously noted methodological limitations of this study.
- 5.8 The Committee considered that overall the evidence demonstrates that MMF is as effective, but less toxic than cyclophosphamide in induction treatment, and as effective as azathioprine in maintenance treatment.
- 5.9 Members noted that unlike in cancer treatment, the distinction between induction and maintenance treatment in lupus is somewhat artificial and it appears that most complete remissions are achieved during maintenance therapy. The Committee noted that in lupus re-induction is often used in severe flare and commonly uses the same induction agent as previously used, however there is no clear guidance on whether patients should be treated with the same maintenance agent repeatedly. Members considered that a proportion of patients on azathioprine maintenance would suffer a renal flare in which case re-induction and maintenance treatment with MMF would be a reasonable treatment option.
- 5.10 The Committee noted that patients who had completed MMF induction who subsequently relapsed following azathioprine maintenance treatment would meet the current 'Initial Application' funding criterion for MMF which require non-transplant patients to have tried and failed steroids, azathioprine and cyclophosphamide (where not contraindicated). However, members noted that the Special Authority system did not permit patients to have more than one initial approval, therefore such patients needed to be managed through a Renewal application as recommended by the Subcommittee.
- 5.11 The Committee considered that 50-60 new patients with Lupus Nephritis would be treated with MMF (induction and/or maintenance) if it were funded as recommended by the Rheumatology Subcommittee. Members considered that discussions with rheumatologists and renal physicians suggested that access to MMF was not really a

big issue and that most patients were already accessing funded MMF, perhaps incorrectly, via the current Special Authority.

- 5.12 The Committee noted that vasculitis is a disease of older population and often cyclophosphamide is used as a preferred agent for induction. Members noted in its previous minutes MMF is inferior to azathioprine in maintenance and hence the previous recommendation with low priority. However, members noted that there will be only few people with vasculitis treated annually therefore having a separate special authority for this condition may not be worthwhile.

6 Gemcitabine for Metastatic Breast Cancer

Application

- 6.1 The Committee considered an application from the Breast Cancer Special Interest Group of the New Zealand Association of Cancer Specialists (BSIG) requesting the funding of gemcitabine for the treatment of patients with metastatic breast cancer (mBC) with gemcitabine to be used at the treating clinician's discretion.

Recommendation

- 6.2 The Committee **recommended** that the application be declined.
- 6.3 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

- 6.4 The Committee noted that breast cancer is the most common cancer in women in many countries and approximately 10% of women present with metastatic disease at the time of diagnosis. Members noted that median survival for metastatic breast cancer (mBC) from the time of diagnosis currently is around 2 years, although some patients experience long-term survival with five-year survival rates around 20%. The Committee noted that metastatic breast cancer remains incurable disease for which the principle aims of treatment are to improve quality of life and prolong time to disease progression.
- 6.5 The Committee noted that current treatment options for patients were determined by patients' tumour characteristics. Members noted that available funded drugs include doxorubicin, epirubicin, paclitaxel, docetaxel, capecitabine, vinorelbine, cyclophosphamide, methotrexate, fluorouracil and cisplatin. Members noted that patients with hormone receptor positive tumours would also be able to access tamoxifen, anastrozole, letrozole and exemestane and that trastuzumab or lapatinib would be offered in patients with HER2 positive tumours.
- 6.6 The Committee noted that the majority of evidence provided in the application comprised small single arm studies of gemcitabine given as monotherapy or in combination with other chemotherapy agents (paclitaxel, docetaxel or platinum) in the

first line setting, and in second and third line settings in patients who have received prior anthracycline and taxane treatment. Members noted that evidence for use of gemcitabine monotherapy was limited to small single arm studies, in which patients had median overall survival of between 8 and 21 months.

- 6.7 The Committee considered that in general these studies demonstrated that earlier use of gemcitabine in the treatment algorithm is associated with longer disease-free intervals but members considered that there was insufficient evidence to demonstrate whether or not this may simply reflect a treatment line effect where median survival times get shorter with subsequent lines of therapy.
- 6.8 The Committee considered that the key evidence comprised two randomised controlled, open label, phase III studies of gemcitabine in combination with other chemotherapy agents.
- 6.9 The Committee noted that the first study (Albain et al J Clin Oncol 2008) compared gemcitabine plus paclitaxel with paclitaxel alone in 529 patients with locally recurrent or mBC who had relapsed following prior treatment with neoadjuvant or adjuvant anthracyclines. Members noted that the patients enrolled in this study had good performance status, which may not be representative of the likely treatment population. Members noted that there was a modest, but statistically significant, improvement in median overall survival in the combination treated group (18.6 months vs. 15.8 months, HR 0.82, 95% CI 0.67-1.0, p=0.0489) and median time to progression and relative response rates were also improved in the combination group. However, members noted that after disease progression additional chemotherapy was permitted at the discretion of clinician and patients in the paclitaxel arm were permitted to cross-over to gemcitabine, members considered that both of these crossovers made any interpretation of OS benefit difficult. Members noted that haematological toxicity, fatigue and neuropathy were more common in the combination treated patients.
- 6.10 The Committee noted that quality of life (QoL) measures from this study were presented at the 2004 American Society of Clinical Oncology meeting and subsequently published in 2012 (Moinpour et al Qual Life Res. 2012 Jun;21(5):765-75). Members noted that patients completed the Rotterdam Symptom Checklist (RSCL) and Brief Pain Inventory (BPI) at baseline and at the end of each treatment cycle. Members noted that only 1 item, the global item score in the Rotterdam scale, demonstrated any difference between the two treatment groups, members noted that this was not a summative measure of the subscales but rather a single question. Members noted that there was no difference between treatment groups for the physical (23 item) psychological (7 item) and activity (8 item) subscales. Members also considered that the open label nature of this study meant that QoL data would likely be open to bias. Members considered QoL improvements were important in the palliative setting but considered that evidence from this study was insufficient to support any extra benefit for the addition of gemcitabine to paclitaxel.
- 6.11 The Committee noted that the second study compared gemcitabine plus docetaxel (GD) with capecitabine-docetaxel (CD) in 305 patients with locally advanced or mBC who had relapsed following one prior treatment with anthracyclines (neo/adjuvant or first line metastatic setting) (Chan et al J Clin Oncol 2009). Members noted that there was no significant difference in progression free survival or response rates between the two treatment groups. However, members noted that duration of overall response was

significantly longer in the CD arm (9.07 months vs 7.75 months $p=0.047$) and considered that, whilst not statistically significant, there appeared to be a trend towards greater overall survival in the CD treated patients.

- 6.12 The Committee noted that in the Chan study haematological toxicity was similar between the two treatment groups with the exception of grade 3/4 leucopenia which was higher in the GD treated patients (78% vs 66% $p=0.025$). More patients in the GD arm received transfusions (17% vs. 7 % $p=0.0051$), erythropoietin and GCSF treatment although there were no statistically significant differences in rates of grade 3/4 neutropaenia, febrile neutropaenia or anaemia. More patients in the CD arm experienced diarrhoea, hand foot syndrome and mucositis. Members noted that there was no difference in QoL measures between the two arms in the study.
- 6.13 The Committee considered that the evidence for benefit of capecitabine was stronger in terms of clinically significant outcomes, despite its toxicity profile and being an oral treatment it was a more convenient for patients.
- 6.14 Overall the committee considered that the strength and quality of the evidence was weak to moderate. Members considered that there was no clear evidence of a clinically significant benefit in terms of overall survival or quality of life for gemcitabine compared with other currently funded treatment options. Members further noted that gemcitabine was associated with significant toxicity particularly haematological toxicities.
- 6.15 The Committee considered that if gemcitabine was funded for mBC it would be used in most patients in addition to currently funded treatment options either in combination or as an additional line of monotherapy treatment in approximately 60-70 patients per annum. Members considered that it would likely increase the requirement for haematological supportive care and increase infusion costs for DHBs with little evidence for QALY gains.
- 6.16 The Committee noted that whilst it didn't support the funding of gemcitabine in mBC specifically it did support the removal of the Special Authority criteria from gemcitabine, and some other cancer treatments, as recommended by the Cancer Treatments Subcommittee.

7 Capsaicin Topical Cream for Osteoarthritis

Application

- 7.1 The Committee considered an application from AFT Pharmaceuticals for the funding of capsaicin 0.025% cream (Zostrix) for the symptomatic relief of pain associated with osteoarthritis not responsive to paracetamol and where NSAIDs are contraindicated.

Recommendation

- 7.2 The Committee **recommended** that capsaicin 0.025% cream be funded on the Pharmaceutical Schedule for the symptomatic relief of pain associated with osteoarthritis not responsive to paracetamol and where NSAIDs are contraindicated with a low priority.

- 7.3 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* (vii) *The direct cost to health services users.*

Discussion

- 7.4 The Committee noted that an application for listing capsaicin cream 0.025% and 0.075% had originally been reviewed and declined by PTAC in November 2002. Members further noted that at its October 2011 meeting the Rheumatology Subcommittee of PTAC had reviewed topical products for joint and muscular pain and recommended that PHARMAC staff take the capsaicin cream 0.025% application back to PTAC for review. The Committee noted there were a number of studies included in the application that had not been previously reviewed by PTAC previously. The Committee noted that capsaicin 0.075% cream is funded under endorsement for post-herpetic neuralgia and diabetic peripheral neuropathy.
- 7.5 The Committee noted that capsaicin is extracted from plants of the genus *Capsicum* and that the effect is short acting requiring applications four times a day. In addition, members noted that the treatment requires regular application for some time to gain full analgesic effect. The Committee noted that for this reason the supplier did not think it likely that capsaicin 0.025% cream will be used to treat sports injuries however, the Committee considered that there was a potential risk for creep into sports injuries and other acute/semi-acute injuries. The Committee noted that capsaicin cream 0.025% is currently available over the counter at a price to the patient of around \$20.00 for a 45 g tube.
- 7.6 The Committee noted that, unlike standard NSAIDs, topically applied capsaicin cream is not associated with any systemic adverse events, such as gastrointestinal (GI) disturbance and increased risk of cardiovascular adverse events. Members noted that approximately 46% of patients experience a mild to moderate burning sensation at the site of application of capsaicin cream which tends to diminish with time, although some patients (about 10%) discontinue treatment because of this.
- 7.7 The Committee considered that the evidence provided was of moderate quality and strength. The Committee noted the results from a double blind placebo controlled study by Altman et al (Seminars in arthritis and rheumatism 1994;23(6):25-33) in which 113 patients with either idiopathic or post-traumatic osteoarthritis of a major joint received either capsaicin 0.025% cream or placebo over a 12 week period. Members noted that no opiates, steroids or NSAIDs were permitted during the study but 3 days a month use of paracetamol for non-arthritic pain was allowed. Members noted that by week 12, 81% of patients on capsaicin had improvement on Clinical Global Evaluation vs 54% on placebo and overall 24% more people on capsaicin had a 50% plus pain reduction than on placebo. Members further noted that the physician's global evaluation and patient's assessment using the visual analogue scale (VAS) pain score both showed statistically significantly better responses to capsaicin cream than placebo.

- 7.8 The Committee noted that Deal et al (Clin Ther 1991;13(3):510-526) also found significant reduction in pain when capsaicin was used in conjunction with standard oral arthritis medications for the treatment of moderate to severe osteo or rheumatoid arthritis knee pain. Members considered that while the study was of short duration (4 weeks) with relatively small numbers (101 patients) it showed a reduction from baseline in the VAS pain score of 57% in the capsaicin group versus 32% in placebo. Members noted that this improvement was statistically significant at all measurement points for both the osteo and the rheumatoid arthritis patients.
- 7.9 The Committee noted the results from a number of other studies, with varying strengths of capsaicin, including McCarthy et al (J Rheumatol 1992;19:4:604-607) who found a 55% reduction in VAS pain score with capsaicin 0.075% compared to placebo and McCleane et al (Br J Clin Pharmacol 2000;49:574-579) who found a statistically significant reduction in chronic neuropathic pain with 0.025% capsaicin versus placebo. Members noted that in a systematic review of topical capsaicin for the treatment of chronic pain, Mason et al (BMJ 2004 Apr 24;328(7446):991) found that for musculoskeletal conditions 38% of patients using capsaicin had at least a 50% reduction in their pain level compared to 25% with placebo with 13% withdrawing because of side effects. The Committee noted that the value of this review was limited as some of the studies included were for conditions other than osteoarthritis.
- 7.10 EULAR Recommendations for both knee and hand osteoarthritis support the use of capsaicin cream for a group of people who are not likely to tolerate NSAIDs but do not get adequate analgesia from paracetamol and non-pharmacological treatments.
- 7.11 The Committee noted that the proposed cost for capsaicin cream (0.025%), although lower than the current OTC cost to patients was higher than the daily cost for NSAIDs, lower than COX2 inhibitors and similar to or lower than opiate options.
- 7.12 The Committee noted that there was significant uncertainty around the potential level of use of capsaicin 0.025% cream but noted that use may be limited by the limited effectiveness, the four times a day dosing requirement and the potential for skin irritation. Members noted that patients with more than one affected joint would require more than one tube per month and therefore costs would increase. Members further considered that compliance with 4 times daily application on affected joints would likely be poor. The Committee considered that there was an unmet need and that a topical treatment may be particularly useful for elderly patients where NSAIDs are contraindicated or where there is significant potential for adverse reactions.

8 Denosumab for Postmenopausal Osteoporosis

Application

- 8.1 The Committee considered an application from Amgen Australia Pty Ltd for the funding of denosumab (Prolia) as second line treatment of osteoporosis in postmenopausal women following bisphosphonate treatment failure or where bisphosphonates are contraindicated.

Recommendation

- 8.2 The Committee **recommended** that the application be declined pending further information about the long term safety of treatment with denosumab.
- 8.3 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

- 8.4 The Committee noted that denosumab is a full-length human monoclonal IgG2 that targets the receptor activator of nuclear factor kappa B ligand (RANKL). The binding to RANKL inhibits the RANKL to RANK interaction which is essential for the formation, function and survival of mature osteoclasts which are responsible for bone resorption. The resultant decrease in bone resorption leads to an increase in bone mass. Denosumab is administered as a single 60 mg subcutaneous injection every 6 months and treatment would be long term.
- 8.5 The Committee noted that the application from the supplier was to list denosumab as second line treatment of osteoporosis in patients who have tried bisphosphonate therapy or where bisphosphonate therapy is contraindicated. The Committee noted that the rationale provided by the company for a second line listing was that denosumab was at least as effective as alendronate and zoledronic acid; has a better side effect profile, is not associated with GI toxicity or acute phase reaction, does not have renal impairment or abnormalities of the oesophagus as contraindications (unlike the bisphosphonates), and has a possible compliance advantage. The Committee also noted that the supplier had commented that PTAC had previously indicated a willingness to consider second line listing of osteoporosis treatments where there is a price differential compared with existing reimbursed treatments.
- 8.6 The Committee considered key evidence from a large double-blind placebo controlled three year follow-up study by Cummings et al for the FREEDOM Trial (NEJM 2009;361:756-765) with radiographic vertebral fracture incidence as the primary outcome. Members noted that the study enrolled 7,868 women with BMD T scores of <-2.5 were randomly assigned to 60 mg denosumab every 6 months for 36 months or placebo. There were statistically significant reductions in vertebral and nonvertebral fractures over the study period and an increase in the BMD in both the lumbar spine and hip ($p < 0.0001$). Members considered that morphometric fractures, the main outcome measure of the study, are a radiological diagnosis and in normal clinical practice many probably would not be diagnosed or treated. The Committee noted that the FREEDOM trial was not suited to the Special Authority requested by the applicant, as it specifically excluded second line patients.
- 8.7 The Committee noted smaller double blind studies including two comparing alendronate with denosumab over 12 months with BMD and bone turnover marker changes from baseline being the outcome variables (Brown et al J Bone Miner Res 2009;24:154-161; Kendler et al J Bone Miner Res 2010;25:72-81). BMD and bone turnover marker improvements were greater with denosumab than alendronate. The Committee noted that the supporting documentation highlighted that denosumab has

not been extensively studied in true second line settings, although the Kendler et al study showed a statistically significant improvement in BMD in patients who transitioned from alendronate (median previous use three years) to denosumab.

- 8.8 The Committee considered that denosumab is a potential immunosuppressive agent due to its mechanism of action and reviewed the risk of cancer and/or infection. The Committee noted that in clinical studies the overall risk of serious adverse events (SAEs) of infection in the primary PMO studies was higher in denosumab than placebo subjects, with 4.1% of denosumab and 3.3% of placebo patients developing a serious infection, although there was no difference in the overall number of infections (serious plus non-serious adverse events) and opportunistic infections were not more common in the denosumab group. The Committee noted that denosumab patients appeared to have a higher incidence of bacterial, cellulitis/erysipelas, abdominal, ear and urinary tract infection.
- 8.9 The Committee noted that, as denosumab is not pharmacologically active in rodents, the carcinogenic potential has not been evaluated in long-term animal studies. The Committee noted that three patients receiving a high dose of denosumab (100 mg 6 monthly) died of a new malignancy and that breast cancer was the most common adverse event leading to discontinuation in the Primary PMO population (0.5% in denosumab vs. 0.3% in placebo). The Committee noted that bone histomorphometry results raised concerns about the degree of bone remodelling suppression and the unknown cumulative effect on the abnormal bone architecture following treatment with bisphosphates if denosumab were to be used second line.
- 8.10 The Committee noted the recommendations of PBAC, NICE and ERG and agreed that zoledronic acid should be the primary comparator and noted that the major differences between denosumab and zoledronic acid were:
- A sub-cutaneous injection six monthly for denosumab vs. an annual intravenous (IV) infusion.
 - The residual effect after discontinuation. Anti-reabsorptive actions of a single dose of IV zoledronic acid have been shown to persist for at least three years in osteopenic postmenopausal women, whereas bone marrow density decreases rapidly following discontinuation of denosumab and any gains made during treatment may be lost within one to two years.
 - Zoledronic acid is less expensive than denosumab, and ongoing trials of zoledronic acid may determine a lower dose of zoledronic acid is the optimal dose further reducing its cost compared to denosumab.
 - Differences in the side effect profiles and contraindications. Zoledronic acid is contraindicated in patients with a creatinine clearance level less than 30 ml per minute. Both products are contraindicated in hypocalcaemic patients. The major side effects of zoledronic acid have been the acute infusion reaction consisting of pyrexia, myalgia and headache (16%, 9% and 8% respectively versus 2%, 2% and 2% in placebo). Denosumab's side effect profile is similar to placebo.

- Only indirect comparisons have been made between zoledronic acid and denosumab as head-to-head trials have not been undertaken. There is no evidence to suggest that denosumab is superior to zoledronic acid for any clinical outcome. Discontinuation rates of 15-20% in trials do not support any adherence advantage claimed in the application

8.11 The Committee considered that they would like to see more long term safety data on denosumab before making a recommendation. The Committee noted that a long term extension of the Cummings et al trial is ongoing and currently at year six without highlighting any additional safety concerns which is encouraging.

9 Testosterone Undecanoate

Application

9.1 The Committee considered a re-application from Bayer Healthcare for the funding of testosterone undecanoate injection (Reandron) for the treatment of testosterone deficiency.

Recommendation

9.2 The Committee **recommended** that testosterone undecanoate injection be listed on the Pharmaceutical Schedule with a low priority.

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, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health services users.*

Discussion

9.4 The Committee noted that PTAC had reviewed an application for this preparation in November 2007. At that time the Committee considered the evidence to be relatively weak and based on a comparison with testosterone enanthate which was unavailable in New Zealand. The Committee acknowledged that testosterone undecanoate injections had a longer duration of action compared to other injectable forms and provide a benefit of reduced injection frequency but noted that the evidence for pharmacokinetic superiority was poor and there was no evidence of additional physiological benefits. At that time, PTAC recommended listing with a low to medium priority but only if cost neutral. The Committee noted that a proposal resubmitted to PHARMAC in February 2011 by Bayer Healthcare did not proceed to PTAC as there was no new clinical evidence.

9.5 The Committee noted that the Hospital Pharmaceuticals Subcommittee of PTAC had reviewed testosterone undecanoate at their October 2011 meeting and considered that all forms of testosterone replacement therapy (including implants and gel) were community based and should only be included in a national PML if listed on the community Pharmaceutical Schedule.

- 9.6 The Committee noted that the further clinical evidence supplied with this proposal was weak and consisted of an observational study from the Waikato Endocrine unit and a literature review by Giaguilli et al (Curr Pharm Design 2011,17;15:1500-1511) and noted that there is still no direct comparative data available.
- 9.7 The Committee reviewed the presentation that had been shown to PHARMAC by the Waikato Endocrine unit and noted that it included an analysis of two years data on the use of testosterone undecanoate injection in Waikato hospital, generated from clinical and nursing notes. The Committee noted that of 254 patients who had been so treated, data from 176 (70%) had been included, with those with less than two years' treatment being excluded, which may be a possible source of bias.
- 9.8 The Committee noted that in the Waikato study, 59% of patients received testosterone undecanoate within a 10-14 week interval and 19% received testosterone undecanoate in an interval of less than 10 weeks; overall trough testosterone levels were in the normal range; haemoglobin and haematocrit levels significantly increased over 2 years and 13% of men had a significant rise in their PSA levels. A significant decrease in mean total cholesterol was noted between the start and one year of treatment but there were no significant changes in HDL, LDL or TG.
- 9.9 The Committee noted that in a subgroup of 21 men who had used testosterone esters and then testosterone undecanoate, treatments were more frequent with testosterone esters than testosterone undecanoate (2.8 weeks vs. 12.3 weeks) and the testosterone levels were more varied with testosterone esters than testosterone undecanoate (1.6-54 nmol vs. 6-9 nmol) although the scatter plots were difficult to interpret.
- 9.10 The Committee noted that while the Waikato experience suggested that overall men had an improved physical and emotional wellbeing, their partners preferred them on this treatment, it was well tolerated and more convenient with fewer doctor visits and less time off work; however there was no clinical data to confirm these observations. The Committee considered the financial slides suggested that Reandron was relatively cost effective compared to other treatments but noted that the practice nurse cost was too high and the patients' costs were not validated.
- 9.11 The Committee reviewed Giaguilli's 2011 review of testosterone replacement therapies with a focus on new therapies and noted that it did not include testosterone mixed esters and concluded that large scale prospective studies or randomised controlled trials are still lacking. Giaguilli concluded that trials that have been done are poorly designed and not adequately powered to detect effects on clinically significant endpoints such as CV disease, bone fractures, cognitive functions, quality of life, frailty and mortality and meta-analysis have only reported a "fair" improvement in sexual function and body composition.
- 9.12 The Committee noted that although testosterone undecanoate provides acceptable efficacy and safety with a smooth pharmacokinetic profile, no head to head studies comparing testosterone undecanoate to testosterone esters and no published comparisons with other currently funded preparations were provided. The Committee considered that without evidence of superiority, or inferiority, any funding decision should be based on a cost minimisation analysis.

10 Azithromycin for Pertussis, Neonatal Conjunctivitis and Pneumonia

Application

- 10.1 The Committee considered an application from Paediatricians from Starship Hospital for the listing of azithromycin suspension for pertussis and neonatal Chlamydia conjunctivitis and pneumonia.

Recommendation

- 10.2 The Committee **recommended** that azithromycin suspension be listed for pertussis and neonatal Chlamydia conjunctivitis and pneumonia with a high priority.
- 10.3 The Committee **noted** that a listing for azithromycin suspension for pertussis would need to occur within the next one to two months as New Zealand is currently approaching a pertussis epidemic.
- 10.4 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

Pertussis

- 10.5 The Committee noted that pertussis is a notifiable disease in New Zealand. Members noted that pertussis is highly contagious, particularly with overcrowding, and is spread by droplets from infected individuals. Members noted that in adults the disease is relatively mild, with a prolonged cough lasting for some months. The Committee noted that in young infants the disease can be devastating with infected babies spending weeks in hospital with intermittent respiratory distress and profound apnoeas. It is young infants that are most at risk of hospitalisation and death. Members noted that New Zealand's rate of pertussis hospitalisations was three to six times higher than those of Australia, USA and UK.
- 10.6 The Committee noted that New Zealand had two previous pertussis epidemics in the last 12 years and that it was likely that the country was on the brink of a third epidemic. Members noted the Environmental Science report (Pertussis report, weeks 16-17 2012, ESR) for late April which showed a total of 1568 cases of pertussis notified in New Zealand for the year to 27 April 2012, compared with 220 at the same time in 2011. Members noted that recently health care worker was identified as positive for pertussis resulting in 200 mother/baby pairs contacted regarding prophylaxis.

- 10.7 The Committee considered that the most effective strategy for pertussis was immunisation, however not all children were immunised or immunised in time. Members noted that a macrolide administered early in the course of the illness can reduce the duration and severity of symptoms and lessen the period of communicability.
- 10.8 Members noted that approximately 80-90% of patients with untreated pertussis would spontaneously clear *Bordetella pertussis* from the nasopharynx within three to four weeks from the onset of cough. Members noted that untreated and unvaccinated infants may remain culture positive for greater than six weeks (MMWR December 9, 2005 / 54(RR14); 1-16).
- 10.9 Members noted a paper from Cooper et al (Arch Ped Adol Med 2002;156:647-50) of a retrospective cohort study of over 300,000 infants born in Tennessee that determined the risk of pyloric stenosis associated with timing of erythromycin use. The incidence of pyloric stenosis was 2.6 per 1000 infants. Erythromycin exposure before 90 days of age was associated with an adjusted rate ratio of 2.05 (95% CI 1.06-3.97), exposure prior to 14 days of life was associated with a rate ratio of 7.88 (1.97-31.57). Members noted that overall the numbers of infants exposed to erythromycin was small in the study, but considered that the findings were consistent with other studies,
- 10.10 Members noted the paper from Honein et al. (Lancet 1999;354:2101-5), a cohort study, which showed erythromycin prophylaxis was causally associated with pyloric stenosis (seven cases out of 157 erythromycin exposed infants vs. zero cases out of 125 infants with no erythromycin exposure. Exposure to erythromycin was associated with an absolute risk of 4.5%.
- 10.11 The Committee noted that hypertrophic pyloric stenosis causes projectile non-bilious vomiting in the first few months of life. Pyloric stenosis typically presents at around 4 to 6 weeks of age and is treated with an operation to split the hypertrophied tissue at the pylorus. Pyloric stenosis is associated with risk of severe electrolyte abnormalities (although this is now relatively rare due to early diagnosis) and the risks and costs of hospitalisation, general anaesthetic and surgery in young infants.
- 10.12 The Committee noted a Cochrane review by Altunaiji et al (Cochrane Database System Review 2007) which reviewed antibiotics for treatment and prophylaxis of pertussis. Members noted that the data was not separated by the age of children enrolled and that four of the studies specifically excluded neonates.
- 10.13 In three trials meta-analysis was undertaken which compared short-term vs. long-term antibiotic treatment. The reviews main conclusions were that antibiotic treatment is effective in eliminating pertussis from the nasopharynx and thus rendering participants non-infectious, but that it did not alter the clinical course of the illness.
- 10.14 Members noted that the meta-analysis comparing short term vs. long term antibiotics showed that there was no significant benefit of long-term antibiotic treatment (10 to 14 days with erythromycin estolate or unspecified salt of erythromycin) compared to short-term antibiotic treatment (azithromycin for three to five days, erythromycin estolate for seven days, or clarithromycin for seven days) in microbiological eradication of *B. pertussis* (RR 1.01; 95% CI 0.98 to 1.04). Meta-analysis showed that fewer side effects were reported in those receiving short-term antibiotic treatment compared to those

receiving long-term antibiotic treatment (14 days of erythromycin) (RR 0.66; 95% CI 0.52 to 0.83).

- 10.15 The Committee noted that the Cochrane review reported a lack of uniformity in the monitoring of side effects and compliance of patients, thus results were just reported by individual trials. Members noted that compliance was better in those children who received azithromycin compared to those who received erythromycin estolate (RR 1.63; 95% CI 1.45 to 1.85) (Langley 2004); fewer side effects were noted with azithromycin (three days) compared with erythromycin (14 days) (RR 0.38; 95% CI 0.19 to 0.75) (Bace 2002); and fewer gastrointestinal adverse effects were noted with azithromycin (five days) compared with erythromycin estolate (10 days) (RR 0.46; 95% CI 0.34-0.62) (Langley 2004).
- 10.16 The Committee considered that azithromycin was likely to be as effective as erythromycin for the treatment and prophylaxis of pertussis. Members considered that azithromycin was also less likely to cause pyloric stenosis in children aged less than four weeks of age. Members considered that there would likely be less negative investigations for pyloric stenosis undertaken in infants taking macrolides if azithromycin is used instead of erythromycin due to the reduction in risk. Neonates are investigated with an ultrasound scan for possible pyloric stenosis based mainly on suggestive history and presence of risk factors, of which erythromycin use is a well established risk factor amongst clinicians.
- 10.17 The Committee noted that pertussis hospital admissions are strongly influenced by ethnicity and social deprivation. Members noted that in the last New Zealand epidemic in 2004/5 the rate of Maori and Pacific hospitalisations was 2.5 and 3.1 respectively compared to Europeans and other ethnicities. The relative risk of hospitalisation for an infant living in the most deprived quintile was 3.7 (2.6-5.2) (Immunisation Handbook 2011, Ministry of Health).
- 10.18 The Committee noted that if PHARMAC intended to list azithromycin suspension for pertussis treatment and prophylaxis then that listing should occur rapidly, as the public health need was high due to the large number of notified cases. Members considered that a listing should occur in the next month or two following this meeting to provide the greatest benefit.
- 10.19 The Committee recommended that azithromycin suspension for pertussis be listed with a high priority under the following restriction:
- Patient has pertussis and this has been notified to the Medical Officer of Health; or
 - Patient has had direct contact with a notified case of pertussis and requires prophylaxis.

Neonatal conjunctivitis and pneumonia

- 10.20 The Committee noted that infants born vaginally to mothers with Chlamydia are at risk of acquiring both conjunctivitis and pneumonia. Members noted that conjunctivitis develops 5-12 days after birth in up to 50% of exposed neonates, although the figure maybe lower than this with Rosenman et al. (Arch Ped Adol Med 2003;157:565-71)

reporting an incidence of 15% across 13 studies in 1055 exposed infants. Members noted that approximately 50% of these infants would also develop pneumonia at 1-3 months of age. Due to nasopharyngeal colonisation with Chlamydia, treatment for the conjunctivitis needs to be systemic rather than topical in order to achieve clearance. Members noted that both the mother and partner would require treatment (with azithromycin tablets).

- 10.21 The Committee noted that the efficacy of erythromycin for chlamydia conjunctivitis and pneumonia is reported to be 85% Rosenman et al. (Arch Ped Adol Med 2003;157:565-71), thus requiring follow-up and repeat treatment in up to a 1/5th of cases.
- 10.22 The Committee noted that the Centres for Disease Control and Prevention (CDC) recommend azithromycin or doxycycline as first line treatment for Chlamydia in sexually active adults. Erythromycin is recommended only as a second line agent, as it is thought to be less efficacious mainly due to gastro-intestinal adverse events leading to non-compliance but also possible due to increasing resistance. New Zealand guidelines recommend azithromycin as it is a one-dose treatment.
- 10.23 Members considered that the arguments regarding pyloric stenosis and gastrointestinal adverse events and compliance in favour of azithromycin are also applicable in this population of neonates treated for Chlamydia. The increased risk of pyloric stenosis with erythromycin is of importance, as these infants would generally present, and are started on treatment, prior to 14 days of age.
- 10.24 The Committee noted the body of evidence for azithromycin for chronic chlamydial trachoma (chronic follicular keratoconjunctivitis) in the Third world. Members noted that the CDC and the American Academy of Pediatrics (AAP) recommend erythromycin for chlamydia conjunctivitis in the United States, based on a paucity of evidence for azithromycin use for this indication. There has only been one small cohort study reported in the literature of azithromycin use in neonatal conjunctivitis from the Developed world, Hammerschlag et al. (PIDJ 1998;17:1049-50), which used azithromycin in 13 culture positive infants with conjunctivitis. Five infants received a single dose, in whom 3 improved clinically and were subsequently culture negative, eight infants received 3 days of treatment in whom 6 improved clinically and were subsequently culture negative, 1 improved clinically but remained culture positive, and one was lost to follow-up.
- 10.25 The Committee noted that the AAP recommend five days of azithromycin or 14 days of erythromycin for treatment of chlamydial pneumonia.
- 10.26 The Committee noted the ESR data from 2010 which showed that 104 cases of chlamydia were reported in patients aged less than 1 year of age in 2010. In New Zealand chlamydia conjunctivitis is treated on the basis of a positive swab from the infant or occasionally positive swab from the mother in an infant with persistent conjunctivitis not improving with topical treatment.
- 10.27 The Committee noted that laboratory and sexual health clinic surveillance data from 2010 (ESR) show that chlamydia is our most common sexually transmitted infection with a national rate of 782 per 100,000, with the highest rate in 15-19 year olds of 3,881 per 100,000. Members noted that rates of chlamydia in Māori are approximately

three times that of Europeans, and Pacific people's rates are 2.2 to 3.7 times European rates.

10.28 The Committee recommended that azithromycin suspension for neonatal conjunctivitis and pneumonia be listed with a high priority under the following restriction:

- Patient has laboratory proven neonatal Chlamydia conjunctivitis or pneumonia.

11 Sildenafil for Raynaud's Phenomenon

Application

11.1 The Committee reviewed a memorandum from PHARMAC staff discussing the funding of sildenafil for Raynaud's Phenomenon.

Recommendation

11.2 The Committee **recommended** that sildenafil be funded with a high priority via Special Authority for 6 months initially (with 6 monthly renewals) for patients with Secondary Raynaud's Phenomenon who have severe digital ischaemia (defined as severe pain requiring hospital admission or with a high likelihood of digital ulceration; digital ulcers; or gangrene) following lifestyle management (avoidance of cold exposure, sufficient protection, smoking cessation support, avoidance of sympathomimetic drugs) and who are refractory to calcium channel blockers and nitrates (or these are contraindicated/not tolerated).

11.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand and (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things.*

Discussion

11.4 The Committee noted that the evidence supporting the use of sildenafil in Raynaud's Phenomenon (RP) was limited to small studies and case reports for Secondary RP.

11.5 The Committee noted a double-blind, placebo-controlled, fixed-dose, crossover study by Fries et al. (Circulation. 2005;112:2980-2985) of 16 patients with symptomatic secondary RP resistant to vasodilatory therapy who were treated with 50 mg sildenafil or placebo twice daily for 4 weeks. The Committee noted that sildenafil significantly reduced the mean frequency of Raynaud attacks, the cumulative attack duration and the mean Raynaud's Condition Score. The Committee also noted that in six patients with Secondary RP and chronic digital ulcerations, trophic lesions began to visibly heal during treatment with sildenafil with ulcerations completely disappearing in two patients although they reappeared or progressed after treatment was stopped.

11.6 The Committee noted a pilot study of 19 patients with systemic sclerosis assessing the effect of sildenafil on digital ulcer healing and related clinical symptoms by Brueckner et al. (Ann Rheum Dis 2010;69:1475-1478). The Committee noted that treatment with the maximally tolerated sildenafil dose (up to 150 mg) for a maximum of 6 months reduced

the number of digital ulcers from 49 at baseline to 17 at the end of treatment as well as significantly improving clinical symptoms.

- 11.7 The Committee noted a double-blind, placebo-controlled study assessing the effect of sildenafil in 57 patients with RP secondary to limited cutaneous systemic sclerosis by Herrick et al. (Arthritis & Rheumatism 2011;69:775-782) where patients received modified-release sildenafil 100 mg once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days or placebo. The Committee noted that the patients experienced a reduction in Raynaud attacks although other clinical symptoms such as duration of attacks were not affected. However the Committee considered that it was difficult to draw conclusions with the short-acting preparation as the long-acting preparation resulted in a 10-fold reduction in the average maximum plasma concentration and a lower area under the curve than the short-acting preparation.
- 11.8 The Committee also noted correspondence from the New Zealand Rheumatology Association supporting the use of sildenafil in severe or refractory RP following failure of calcium channel blockers and as an alternative to iloprost.
- 11.9 The Committee noted a review by Baumhake and Bohm (Vascular Health Risk Management 2010;6:207-214) which included a treatment algorithm restricting sildenafil use to Secondary RP following calcium channel blockers and/or nitrates in patients with severe ischemia or digital ulcers and following calcium channel blockers and/or nitrates in patients with a stable condition.
- 11.10 The Committee considered that there was a lack of treatment options for patients with severe disease, that severe disease occurred with Secondary RP and that there would be perhaps 100 such patients nationally. The Committee considered that severe RP is a disabling disease, sildenafil would provide a clinical benefit in patients with severe Secondary RP, and would also likely reduce costs associated with ulcers and amputation.
- 11.11 The Committee noted that bosentan had been trialled in digital ulcers but considered that the results were not encouraging as there was no effect on digital ulcer healing (Matucci-Cerinic & Seibold. Rheumatology 2008;47:v46-v47; Matucci-Cerinic et al. Ann Rheum Dis 2011;70:32-38).