

PTAC meeting held on 1 & 2 August 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.

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. Matters Arising.....	3
2. Subcommittee minutes.....	4
3. Correspondence.....	5
4. Nab-paclitaxel for metastatic breast cancer.....	6
5. Abiraterone for castrate-resistant metastatic prostate cancer.....	10
6. Sodium valproate – possible brand switch.....	13
7. Vitamin D for the prevention and treatment of vitamin D deficiency in pregnancy and infancy.....	18
8. Rotavirus vaccine.....	20
9. Varicella vaccine.....	26
10. Human Papilloma Virus vaccine (HPV) for males.....	30

1 Matters Arising

1.1 Enzyme Replacement Therapies paper

1.1.1 The Committee considered evidence from a single centre, prospective, open-label cohort study by De Vries et al. (Orphanet J Rare Dis 2012;73:1-10) that was provided by a member of the public. The study followed 69 patients who were treated with alglucosidase alfa for a median of 23 months and assessed muscle strength, muscle function, and pulmonary function every 3 to 6 months.

1.1.2 The Committee considered two of the five outcome measures, Quick Motor Function Test (QMFT) and Forced Vital Capacity (FVC) supine, to be the most clinically relevant. A member noted papers by van Cappell (Inherit Metab Dis. 2012;35(2):317–323) and Fromageot et al. (Arch Phys Med Rehab 2001;82(1):123-8) which considered QMFT to be a well-validated measure that tests muscle strength and function, and FVC in supine position to be the most sensitive measure of diaphragmatic weakness.

1.1.3 The Committee noted that patients showed small improvements in some surrogate measures of muscle and pulmonary function, but the average changes in Quick Motor Function Test (QMFT) scores were unchanged and during treatment the Forced Vital Capacity (FVC) in supine position declined.

1.1.4 The Committee considered that this paper did not provide sufficient evidence to warrant a change in its previous recommendations to decline funding for alglucosidase alpha.

1.2 Clinician correspondence relating to rituximab in MPO-ANCA associated vasculitis

1.2.1 The Committee noted correspondence received from a renal physician, on behalf of the New Zealand Rheumatology Association, with regards to rituximab in MPO-ANCA associated vasculitis.

1.2.2 The Committee noted that it had previously reviewed rituximab for this indication at its February and May 2013 meetings. The Committee also noted that it had recommended in May 2013 that rituximab should only be funded for patients with MPO-ANCA associated vasculitis after mycophenolate mofetil has been trialled and proven ineffective.

1.2.3 The Committee considered that the current correspondence did not specifically address whether mycophenolate mofetil is inferior to rituximab in the MPO-ANCA patient group. The Committee noted that in February 2013 it had considered that the available evidence for MMF in patients with MPO-ANCA positive vasculitis was as good as that for rituximab in that indication. The Committee considered that there was no reason for it to change its recommendation for rituximab in this patient group.

- 1.2.4 The Committee noted that long term data from the RAVE study (Specks et al. N Engl J Med 2013; 369:417-427) has recently been published. The Committee noted that PHARMAC is in the process of establishing a Nephrology Subcommittee. The Committee recommended that this funding application for rituximab in MPO-ANCA associated vasculitis is referred to that Subcommittee for its advice.
- 1.3 The Committee noted the two items of correspondence from Pfizer and GSK regarding the Minutes of the Immunisation Subcommittee and providing further submissions on the pneumococcal conjugate vaccines.

2 Subcommittee Minutes

2.1 Immunisation Subcommittee – 23 April 2013

2.1.1 The Committee noted and accepted items 1, 3 and 4.

2.1.2 Regarding recommendation at 5.10 in the Immunisation Subcommittee minutes: “The Subcommittee recommended that all vaccines discussed in the General review should include an allowance for revaccination of up to the entire number of vaccines for patients who have undergone HSCT, solid organ transplant or chemotherapy, with a high priority. The Subcommittee considered that a restriction broadly along the following lines for each vaccine would be appropriate:

An additional dose(s) (as appropriate for the various vaccines) are funded for (re-)immunisation for patients post HSCT, or chemotherapy; pre- or post splenectomy; pre- or post- solid organ transplant, renal dialysis and other severely immunosuppressive regimens”

The Committee considered that the terminology could be more specific in relation to ‘chemotherapy’, to confine this to cancer chemotherapy and other immunosuppressive treatments continued for more than 4 weeks.

2.1.3 Regarding the recommendation of 5.12 on varicella vaccination and immunocompromised patients, the Committee deferred discussion until the broader discussions of varicella later in the meeting.

2.1.4 The Committee noted and accepted items 6, 7, 8 and 9.

2.2 Cancer Treatments Subcommittee (CaTSoP) – 22 March 2013

2.2.1 The Committee noted and accepted items 1 to 9, excepting items 3.5, 6.9, 8.11 and 8.12.

2.2.2 Regarding item 3.5, the Committee agreed with CaTSoP's recommendation that carboxypeptidase G2 be included on the Hospital Medicines List (HML), but considered that the access criteria will need to be better defined. The Committee considered that the wording of the restriction criteria could reflect the protocol used by Auckland Hospital. Regarding item 6.9, the Committee deferred making a recommendation for bortezomib retreatment in multiple myeloma until after CaTSoP had reviewed the funding application and provided a recommendation for lenalidomide as 2nd and 3rd line treatment in multiple myeloma. The Committee noted that CaTSoP will review this lenalidomide application at the Subcommittee's meeting in September 2013.

2.2.3 Regarding item 8.11 and 8.12, the Committee maintained its previous recommendation that dexrazoxane be funded only for paediatric patients enrolled in a clinical trial. The Committee maintained its previous recommendation that the funding of dexrazoxane for adult patients and paediatric cancer patients not participating in a clinical trial, including those treated as per trial protocols, be declined.

2.3 Respiratory Subcommittee – 24 May 2013

2.3.1 The Committee noted and accepted items 1 to 5 excepting item 5.9.

2.3.2 Regarding item 5.9, the Committee was unable to endorse the Respiratory Subcommittee's recommendations in regard to changes to the Special Authority criteria for tiotropium. The Committee considered that COPD is poorly diagnosed in the community and that accurate spirometry measurements are imperative to diagnosis. The Committee considered that PTAC would need to review the data before accepting the Subcommittee's recommendation.

2.3.3 Regarding item 6, the Committee noted that the application to list omalizumab had previously (2007) been recommended for decline by the Subcommittee and PTAC. The Committee noted that the Respiratory Subcommittee had reviewed an updated application from the supplier and had now recommended listing with a medium priority. The Committee considered that, due to the cost of treatment with omalizumab, it would need to review the data before making a recommendation.

2.3.4 Regarding item 7, the Committee noted that the Respiratory Subcommittee had recommended that extra fine beclomethasone dipropionate be listed with a medium priority. The Committee considered the application would need to be reviewed by PTAC if the cost of treatment with extra fine beclomethasone dipropionate was not cost neutral to the therapeutically-equivalent inhaled corticosteroids currently listed on the Pharmaceutical Schedule.

3 Correspondence

- 3.1 The Committee noted correspondence from Merck Serono regarding the May 2013 PTAC minutes on cetuximab in k-RAS wild type metastatic colorectal cancer. The Committee noted that the supplier is requesting that PTAC amend its previous minutes that stated that 'the signals of benefit for bevacizumab in this setting were stronger'. The Committee noted that the supplier considered that it had been inappropriate to draw conclusions regarding the relative effectiveness of the two agents when evidence for this comparison had not been presented to the Committee. The supplier also considered that the statement was not supported by evidence.
- 3.2 The Committee however considered that its previous statement related specifically to the patients being down-staged with treatment to enable tumour resection from the liver. The Committee considered that the context of this statement was in fact as above and therefore considered that it would be appropriate for the Committee to maintain its previous statements and recommendations relating to cetuximab in this setting.

4 Nab-paclitaxel for metastatic breast cancer

Application

- 4.1 The Committee reviewed an application from the New Zealand Breast Cancer Special Interest Group (NZBSIG) for the listing of nanoparticle albumin-bound (nab)-paclitaxel on the Pharmaceutical Schedule for the treatment of metastatic breast cancer.

Recommendation

- 4.2 The Committee **recommended** that nab-paclitaxel be listed with a low priority for patients with metastatic breast cancer.
- 4.3 The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) before making a final priority recommendation for advice on:
- 4.3.1 The patient group most likely to benefit;
 - 4.3.2 Whether patients who had an anaphylactoid reaction to a standard paclitaxel preparation (cremophor containing) would be treated with nab-paclitaxel although 'previous hypersensitivity reactions to paclitaxel' is listed as a contraindication in the nab-paclitaxel Medsafe datasheet;
 - 4.3.3 The appropriate Special Authority criteria; and
 - 4.3.4 The expected gain in overall survival from the availability of a second-line of taxane therapy for patients who had an anaphylactoid reaction to standard paclitaxel.

The Decision Criteria particularly relevant to these recommendations are: (i) *The health needs of all eligible people within New Zealand*; (ii) *Maori and Pacific people* (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

- 4.4 The Committee noted that it had previously reviewed a funding application in November 2010 from the supplier for nab-paclitaxel in metastatic breast cancer after failure of prior therapy including an anthracycline. Following receipt of advice from the Cancer Treatments Subcommittee (CaTSoP), the Committee noted that it (PTAC) had previously recommended that nab-paclitaxel be funded for this patient group only if cost-neutral to weekly paclitaxel and 3-weekly docetaxel.
- 4.5 The Committee noted that this current funding application from NZBSIG was for the following patient groups:
- 4.5.1 All patients with metastatic breast cancer indicated for a taxane (preferred option); but particularly for
 - 4.5.2 Patients with a history of an anaphylactoid reaction to the standard paclitaxel preparation due to the cremaphor EL, the formulation vehicle in the preparation; and
 - 4.5.3 Patients with contraindications to the pre-medications required for standard taxanes e.g. patients with diabetes in whom glucose control can be significantly destabilised by high dose corticosteroids.
- 4.6 The Committee noted that because it is very hydrophobic, paclitaxel requires solvents like Cremophor EL to enable it to be parenterally administered. The Committee noted that Cremophor EL contribute to some of the main toxicities seen with standard paclitaxel including anaphylactoid reactions. The Committee noted that this was different to anaphylactic reactions but the two reactions may be difficult to distinguish clinically. The Committee noted that to prevent or limit the severity of the anaphylactoid reactions, patients are pre-medicated with glucocorticosteroids and antihistamines. The Committee noted that nab-paclitaxel does not contain Cremophor EL and therefore premedication with corticosteroids and antihistamines is not recommended in the data sheet.
- 4.7 The Committee noted that the evidence for the efficacy of nab-paclitaxel presented in the application was of moderate/good quality but weak strength for clinical outcomes.
- 4.8 The Committee noted a study by Gradishar et al (JCO 2005;23 (31):7794-803) which compared nab-paclitaxel with polyethylated castor oil-based standard paclitaxel in patients with metastatic breast cancer (MBC). Patients were randomly assigned to 3-week cycles of either nab-paclitaxel 260 mg/m² intravenously without premedication (n = 229) or standard paclitaxel 175 mg/m² intravenously with

premedication (n = 225). The Committee noted nab-paclitaxel demonstrated significantly higher response rates compared with standard paclitaxel (33% v 19%, respectively; P = .001) and significantly longer time to tumour progression (23.0 v 16.9 weeks, respectively; hazard ratio (HR) 0.75; P = 0.006).

- 4.9 The Committee noted a study by Rugo et al (ASCO MEETING ABSTRACTS Jun 21, 2012) which was a randomised phase III trial of weekly paclitaxel compared with nab-paclitaxel or ixabepilone with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Patients were randomised 1:1:1 to receive paclitaxel (90 mg/m²), ixabepilone (16 mg/m²) or nab-paclitaxel (150 mg/m²) on a 3 week on, 1 week off schedule, stratified by prior adjuvant taxane use and hormone receptor status. The Committee noted that median progression-free survival (PFS) was 10.4, 9.6 and 7.6 months for paclitaxel, nab-paclitaxel and ixabepilone, with HRs (95% CIs) of 0.94 (0.73-1.22) and 0.66 (0.51-0.84) for paclitaxel to nab-paclitaxel and ixabepilone respectively.
- 4.10 The Committee also noted a study by Guan et al (Asia-Pacific J Clin Onc 2009;5:165–174) which was not provided by the applicants but located by a PUBMED search for randomised controlled trials of nab-paclitaxel. This was an open-label, multicentre study where 210 patients with metastatic breast cancer were randomly assigned to receive nab-paclitaxel 260 mg/m² intravenously (i.v.) over 30 min every 3 weeks (q3w) with no premedication or paclitaxel 175 mg/m² i.v. over 3 h q3w with standard premedication. The Committee noted the overall response rate was 54% and 29% in patients treated with nab-paclitaxel and paclitaxel, respectively (P < 0.001). Nab-paclitaxel induced a higher response rate in patients who were <65 years old, patients who were receiving first-line therapy, patients who had no prior anthracycline therapy, patients who had ≤ or >3 metastatic lesions, and patients who had visceral disease. Members noted that the PFS period was 7.6 months for nab-paclitaxel and 6.2 months for paclitaxel (P = 0.118).
- 4.11 The Committee noted a study by Gradishar et al (JCO 2009;27:3611-3619) which was a phase II study that examined the antitumor activity and safety of weekly and 3-weekly (q3w) nab-paclitaxel compared with docetaxel as first-line treatment in patients with metastatic breast cancer. In this randomised, multicentre study, patients (n = 302) with previously untreated metastatic breast cancer received nab-paclitaxel 300 mg/m² q3w, 100 mg/m² weekly, or 150 mg/m² weekly or docetaxel 100 mg/m² q3w. The Committee noted that nab-paclitaxel 150 mg/m² weekly demonstrated significantly longer PFS than docetaxel by both independent radiologist assessment (12.9 vs. 7.5 months, P = .0065) and investigator assessment (14.6 vs. 7.8 months; P = .012). The study involved independent radiologist assessment and investigator assessment. Members noted that on the basis of independent radiologist review, both 150 mg/m² (49%) and 100 mg/m² (45%) weekly of nab-paclitaxel demonstrated a higher overall response rate (ORR) than docetaxel (35%), but this did not reach statistical significance. This trend was also supported by statistically significant investigator-assessed ORR for both weekly nab-paclitaxel doses versus docetaxel.
- 4.12 The Committee noted that in the one study that presented information about quality of life, there was no difference between nab-paclitaxel and paclitaxel (Gradishar et al. JCO 2005;23:7794-803). The Committee noted that the incidence of peripheral neuropathy was higher with nab-paclitaxel than standard paclitaxel but the incidence of neutropenia was lower with nab-paclitaxel.

- 4.13 The Committee noted that 40% of patients experience an anaphylactoid reaction with standard paclitaxel preparations if they do not receive premedication and about 75% of these patients experience a reaction at the first dose (Gelderbom et al. Eur Cancer 2001; 37 (13): 1590-98 and Tyson LB et al. ASCO Annual Meeting 1999;18:585a-abstract 2260). The Committee noted that the occurrence of severe anaphylactoid reactions to standard paclitaxel is reduced to approximately 2% of patients if they are pre-medicated (Taxol Medsafe datasheet). The Committee noted that the occurrence of hypersensitivity reactions with nab-paclitaxel was approximately 1% (Abraxane Medsafe datasheet). The Committee considered that anaphylactoid reactions were serious, with fatalities even in patients premedicated with steroids and antihistamines. The Committee also noted that the Medsafe datasheet for nab-paclitaxel (Abraxane) states that nab-paclitaxel should not be used in patients who have exhibited hypersensitivity reactions to paclitaxel. The Committee considered that the benefits of nab-paclitaxel also include a shorter infusion time and the removal of the requirement to pre-medicate with corticosteroids and antihistamines.
- 4.14 Members noted that there is no specific evidence of harm or benefit of tighter control of blood glucose in relation to chemotherapy when patients are pre-treated with corticosteroids. Members noted that unstable blood glucose levels can result in greater inconvenience and sometimes anxiety in patients undergoing chemotherapy. The unstable blood glucose levels could also require initiating treatment with insulin. The Committee noted that there were other potential adverse effects of corticosteroids, such as dysphoria and hypomania and therefore avoidance of corticosteroids could lessen the burden on patients.
- 4.15 The Committee noted that currently, if patients experience an anaphylactoid reaction to standard paclitaxel, treatment protocols suggest increasing the steroid dose and slowing the infusion rate. If these measures are ineffective, the infusion is abandoned and docetaxel is used instead. The Committee noted that patients with metastatic breast cancer currently receive up to two lines of taxane therapy (paclitaxel and docetaxel). The Committee considered that nab-paclitaxel would provide an additional treatment option in patients who have had an anaphylactoid reaction to standard paclitaxel. The Committee was however unsure how much additional benefit a second line of taxane therapy conferred and referred this issue to CaTSoP for its advice.
- 4.16 The Committee noted that there is a need for improved treatments for metastatic breast cancer that improve quality of life and overall survival. Members noted that Māori patients present later, at a younger age and have a higher mortality from breast cancer compared with non-Māori. The Committee considered that if nab-paclitaxel was funded for all patients with metastatic breast cancer, its usage in New Zealand would be similar to that in Australia where 70% of patients on any taxane were on nab-paclitaxel.
- 4.17 The Committee considered that its recommendation for nab-paclitaxel in metastatic breast cancer was based mainly on its increased safety through the reduced incidence of serious anaphylactoid reactions and reduced need for premedication.

5 Abiraterone for castrate-resistant metastatic prostate cancer

Application

- 5.1 The Committee reviewed a funding application from Janssen for abiraterone (Zytiga) in castrate-resistant metastatic prostate cancer.

Recommendation

- 5.2 The Committee **recommended** that abiraterone be listed on the Pharmaceutical Schedule with a low priority for patients with castrate-resistant metastatic prostate cancer who have received prior chemotherapy containing a taxane.
- 5.3 The Committee also **recommended** that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) for consideration and advice on appropriate Special Authority criteria, potential patient numbers, the impact on abiraterone funding on current treatment algorithms and the Subcommittee's opinion on the place of ketoconazole therapy in this indication.
- 5.4 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; (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

- 5.5 The Committee noted that the supplier has proposed that abiraterone be funded for two subgroups of patients with castrate-resistant metastatic prostate cancer:
- 5.5.1 Patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (taxane-naïve); and
- 5.5.2 Patients who have received prior chemotherapy containing a taxane.
- 5.6 The Committee noted that prostate cancer is characterised by androgen-stimulated growth and that historical first line treatment for metastatic prostate cancer has been "total androgen blockade", comprising testicular suppression with gonadotropin-releasing hormone (GnRH) agonists or surgery, and testosterone blockade with agents such as flutamide and bicalutamide. The Committee noted that eventually however the cancer becomes castration-resistant.
- 5.7 The Committee considered that there is good strength and quality of evidence for the primary clinical finding of improved overall survival with abiraterone versus placebo, especially in the subgroup of patients who have been treated with docetaxel. The Committee noted the key publications and reports for the COU-AA-301 and 302 trials. The Committee considered the trials to be well designed. The Committee noted that COU-AA-301 assessed patients who had received prior chemotherapy and COU-AA-302 assessed patients who were asymptomatic or mildly symptomatic and had not received prior chemotherapy.

- 5.8 The Committee noted that the COU-AA-301 study (N Engl J Med 2011; 364:1995-2005 and Lancet Oncol. 2012;13:983-92) included 1095 patients who were randomised 2:1 to abiraterone plus prednisone or placebo plus prednisone treatment arms. This study was unblinded when a pre-planned interim analysis found an increase in overall survival with abiraterone. The Committee noted the updated report after 20.2 months median follow-up which found an increase in median overall survival from 11.2 months to 15.8 months in patients who received abiraterone. The Committee noted progression free survival (PFS) was: 8.5 months with abiraterone versus 6.6 months with placebo (Fizazii et al. Lancet Oncol. 2012;13:983-92).
- 5.9 The Committee noted that COU-AA-302 included 1088 patients who were randomised 1:1 to abiraterone plus prednisone or placebo plus prednisone treatment arms. This study was unblinded when a pre-planned interim analysis after 22.2 months median follow-up found an increase in PFS from 8.3 months to 16.5 months in the abiraterone arm. Members noted that overall survival median was 27.2 months for placebo and was not reached for abiraterone. This result was less statistically robust because it did not cross the pre-specified O'Brien-Fleming boundary p-value of 0.0008. Members noted that the authors reported a HR of 0.75 ($p=0.01$). (Ryan et al. N Engl J Med. 2013;368:138-48).
- 5.10 Members noted that due to abiraterone's effect as a pan-cytochrome P450 inhibitor, there was a significant potential for drug interactions. The Committee noted that historically ketoconazole has been used for this indication as it had antiandrogenic effects. Members considered that, anecdotally, ketoconazole is not widely used in New Zealand for this indication, and drug interactions may limit its use in some patients. Members noted that ketoconazole was shown in a randomised trial to halve prostate specific antigen (PSA) levels in around 27% of patients but there is no evidence that it prolongs life expectancy (Small, et al (CALGB 9583) JCO 2004; (6) 1025-1033).
- 5.11 Although time to PSA progression was increased from 5.9 to 8.6 months, ketoconazole can result in significant liver and gastrointestinal toxicities as well as cause adrenal insufficiency Nizoral Medsafe datasheet <http://medsafe.govt.nz/profs/datasheet/nizoreltab.pdf>.
- 5.12 The Committee noted that abiraterone would be used in combination with prednisone. The Committee noted that the comparator therapy would be chemotherapy with docetaxel in the taxane-naïve setting and best supportive care or ketoconazole in the post-taxane setting. The Committee noted that in the taxane-naïve setting, abiraterone would not replace docetaxel but it would just delay its use.
- 5.13 The Committee noted the evidence related to the impact of abiraterone on the quality of life of patients (QoL). The Committee considered that this evidence was best developed in the post-docetaxel setting. The Committee noted that Ryan et al reported BPI-SF and FACT-P questionnaire results (ESMO abstract from 2012). The median time to average pain intensity progression was 18.4 months for placebo, and 26.7 months with abiraterone. Members noted that the median time to degradation in the FACT-P score was 8.3 months for placebo and 12.7 months for abiraterone. Members noted that there was no data on the actual QoL scores for these patients, only on time to change.

- 5.14 The Committee noted a study by Logothetis et al (Lancet Oncol. 2012;13:1210-7) which examined the effect of abiraterone and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer. Pain intensity and interference of pain with daily activities were assessed with the Brief Pain Inventory-Short Form questionnaire at baseline, day 15 of cycle 1, and day 1 of each treatment cycle thereafter until discontinuation. The Committee noted that median follow-up was 20.2 months. In patients with clinically significant pain at baseline, abiraterone and prednisone resulted in significantly more palliation (157 of 349 [45.0%] patients vs. 47 of 163 [28.8%]; $p=0.0005$) and faster palliation (median time to palliation 5.6 months vs. 13.7 months, $p=0.0018$) of pain intensity than occurred with prednisone alone. Palliation of pain interference (134 of 223 [60.1%] vs 38 of 100 [38.0%], $p=0.0002$; median time to palliation of pain interference (1.0 months vs 3.7 months, $p=0.0004$) and median duration of palliation of pain intensity (4.2 months vs 2.1 months, $p=0.0056$) were significantly better with abiraterone acetate and prednisone than with prednisone alone. Members noted that median time to occurrence of first skeletal-related event was significantly longer with abiraterone acetate and prednisone than with prednisone alone (25.0 months vs 20.3 months, $p=0.0001$).
- 5.15 The Committee noted a study by Sternberg et al (Ann Oncol. 2013;24:1017-25) which considered the effect of abiraterone on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. The Brief Fatigue Inventory (BFI) questionnaire was used to measure patient-reported fatigue intensity and fatigue interference with activities of daily life. 797 patients were randomised to abiraterone acetate and prednisone, and 398 were randomised to placebo and prednisone. Compared with prednisone alone, in patients with clinically significant fatigue at baseline, abiraterone acetate and prednisone significantly increased the proportion of patients reporting improvement in fatigue intensity (58.1% vs. 40.3%, $p=0.0001$), improved fatigue interference (55.0% vs. 38.0%, $p=0.0075$), and accelerated improvement in fatigue intensity (median 59 days versus 194 days, $p=0.0155$).
- 5.16 The Committee noted a study by Harland et al (2011) (abstract supplied in supplier's submission) which assessed the functional status of patients with metastatic castrate-resistant prostate cancer using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Members noted that median time to decline increased from 253 to 363 days with abiraterone.
- 5.17 The Committee noted a study by Haynes et al (Soc Sci Med. 2008;67:928-37) which reported that Māori and Pacific peoples' ethnicity was strongly associated with poorer survival (after controlling for age and gender), partly because ethnicity was also linked to the likelihood of advanced disease at diagnosis. The report stated that prostate cancer is inequitable, insofar as Māori are more likely to be diagnosed with advanced disease (OR 3.249 $p<0.01$), and more likely to die (OR 1.935 $p<0.01$) even when controlling for stage of disease (OR 1.45, $p<0.01$). The Committee noted that similar statistics also applied for Pacific men, although death risk is related to the stage of disease at diagnosis.
- 5.18 Members considered that abiraterone represented progress in this therapeutic area but also noted the high costs associated with the therapy. The Committee' noted that its recommendation for abiraterone has taken into account the clinical benefit associated

with its use in patients who have been treated with a taxane and the high cost associated with abiraterone funding.

6 Sodium valproate – possible brand switch

Application

- 6.1 The Committee reviewed a request from Te Arai Biofarma for advice on the clinical acceptability of switching from the innovator brand of sodium valproate Epilim EC (sodium valproate, enteric coated) to a generic valproate (sodium valproate, enteric coated)

Recommendation

The Committee **recommended** that generic sodium valproate should **not** be listed as “sole supply” in the Pharmaceutical Schedule

Discussion

- 6.2 The Committee noted that there was an application related to the potential to list generic sodium valproate in the Pharmaceutical Schedule. The Committee noted that the request was for sole supply and that there was the potential for savings to the pharmaceutical budget.
- 6.3 The Committee noted the bioequivalence studies provided and observed that it was Medsafe’s role to consider and determine issues related to bioequivalence. <http://www.medsafe.govt.nz/Profs/PUArticles/Mar2013GenericMedBioequivalence.htm>
- 6.4 The Committee noted Medsafe’s consideration would involve ensuring the drug used in the pharmacokinetic studies (Depakine) is identical to the New Zealand brand (Epilim). It was also noted that there is a difference between ‘bioequivalence’ and ‘interchangeability’.
- 6.5 The Committee expressed its preference for medications to be registered with Medsafe before funding is considered and noted that it was ultimately Medsafe’s role to determine the safety, efficacy and bioequivalence of the medicine. The Committee noted the purpose of this review was to determine the suitability of sole supply and not to determine if the product should be registered.
- 6.6 The Committee noted that the applicant had provided evidence of bioequivalence for Valopin EC with Depakine EC. The Committee noted the single-dose, 2 way cross over bioequivalence study (ACDIMA BioCenter for Bioequivalence and Pharmaceutical Studies, Jordan) of Valopin (EC) 500mg Tablets versus Depakine (EC) 500mg in healthy male volunteers. Members noted that the results of the study were:

6.6.1 In the fed state, the Cmax ratio for VALOPIN EC vs. Depakine EC was 0.95, with a 90% CI 88-103%, and the AUC ratio was 1.00 with 90% CI 94-104%;

6.6.2 In the fasting state, the C_{max} ratio for VALOPIN EC vs. Depakine EC was 0.99, with a 90% CI 94-104%, and the AUC ratio was 0.99 with 90% CI 95-104%.

- 6.7 The Committee noted that the study involved only males and that New Zealand guidelines require both genders in bioequivalence studies. However the studies otherwise complied with the FDA, EMEA and Medsafe guidelines for bioequivalence studies. The Committee considered that the study involving fed volunteers would more likely reflect real life.
- 6.8 Members noted that sodium valproate exhibited non-linear pharmacokinetics and therefore at higher plasma concentrations, the plasma protein binding of valproate becomes non-linear. This leads to higher free fractions of valproate. This may not be equivalent between different preparations of the drug.
- 6.9 The Committee noted that it was important to consider the variability in pharmacodynamics for individual patients exposed to the same dose of different formulations. The Committee noted that in the bioequivalence studies provided that some patients had markedly different AUC, C_{max} and C_{max}/AUC (rate of absorption) with the two formulations. The Committee noted that it would be for Medsafe to determine the clinical significance of this, but considered that a markedly different C_{max} or AUC with a different formulation of the same medication could expose a patient with epilepsy to the risk of break through seizures or adverse effects of that medication.
- 6.10 The Committee noted that there was no empirical evidence on the outcomes of brand switching from Epilim to the generic valproate under discussion. The Committee considered that there would be similar issues in switching between any brand of sodium valproate.
- 6.11 The Committee noted a systematic review by Kesselheim et al (Drugs. 2010;70:605-21) which considered seizure outcomes following the use of generic versus brand-name antiepileptic drugs (AED). Members noted that this systematic review and meta-analysis identified 16 studies (9 RCTs, 1 prospective nonrandomised trial, 6 observational studies). Review authors assessed characteristics of the studies and, for RCTs, extracted counts for patients whose seizures were characterized as 'controlled' and 'uncontrolled'. Seven RCTs were included in the meta-analysis. Members noted that the aggregate odds ratio (n = 204) was 1.1 (95% CI 0.9-1.2), indicating no significant difference in the odds of uncontrolled seizure for patients on generic medications compared with patients on brand-name medications. The Committee noted that by contrast, the observational studies identified trends in drug or health services utilisation that the authors attributed to changes in seizure control.
- 6.12 The Committee noted a systematic review of prospective and retrospective studies related to the generic substitution of antiepileptic drugs by Yamada et al (Ann Pharmacother. 2011; 45:1406-15). The Committee noted that the authors concluded that there is an inconsistency between retrospective and prospective studies of generic AED substitution. The highest levels of evidence indicate that there should not be a problem with generic substitution, although some patients are more prone to problems with the generic products. Members noted that the authors also stated that

there is some evidence suggesting that switches between multiple generic AED products in certain individuals may be problematic.

- 6.13 The Committee noted a literature review by Hakonsen (GaBI Journal 2012;1:28-32) summarising the research on the patients' perspectives of generic substitution in some Western countries between 2000 and 2011, with special emphasis on the challenges these attitudes present for optimal drug use. The 20 studies included in the review indicated that close to one-third of all patients were uneasy about having their drug(s) substituted generically. Between 8% and 34% of patients reported poorer effects and/or new side effects after a change except for antiepileptic drug users, for whom the number of reports was higher. Poor awareness of generics substitution caused confusion and reduced the patients' willingness and ability to take their medication as prescribed. Patients' acceptance of generics substitution was influenced by age, educational levels, perceptions about disease, generic drug information, and who informed them about the change. Members noted that the studies consistently suggested a continuing need for information directed at patients and an increased involvement of physicians. Members noted that the author concluded that although generic substitution is well accepted by the majority of patients, about one-third of the patients report negative experiences that may lead to poor adherence and medication errors.
- 6.14 The Committee noted a systematic review by Talati et al (Pharmacotherapy. 2012;32:314-22) on the efficacy and safety of innovator versus generic drugs in patients with epilepsy. Compared with initiation of innovator antiepileptic drugs, initiation of generic antiepileptic drugs did not significantly alter seizure occurrence (relative risk (RR) 0.87, 95% CI 0.64-1.18) or frequency (standardised mean difference 0.03, 95% CI -0.08 to 0.14; withdrawals due to lack of efficacy (RR 1.02, 95% CI 0.41-2.54) or adverse events (RR 0.79, 95% CI 0.28-2.20), pharmacokinetic concentrations (maximum, minimum, or area under the curve), or multiple adverse events in clinical trials. Members noted that in qualitatively evaluated observational studies, switching between forms of antiepileptic drug (innovator to generic, generic to generic) may have increased the risk of hospitalisation, hospital stay duration and a composite end point of medical service utilisation but may not have increased outpatient service utilisation. Members noted that the reviewers concluded that it appears that initiating an innovator or generic antiepileptic drug will provide similar efficacy, tolerability, and safety but that switching from one form to the other may be associated with more hospitalisations and longer hospital stays.
- 6.15 The Committee noted a retrospective cohort study by Erickson et al (Epilepsia 2011;52:1365-1371) which examined whether switching from select branded to generic AEDs in patients with epilepsy is associated with adverse outcomes. This was a retrospective cohort study, using a large health insurance plan claims database, comparing patients with epilepsy who switched from brand to generic equivalent phenytoin, lamotrigine, or divalproex after 6 months (switch cohorts) to matched patients who remained on the brand (non-switch cohorts). Primary outcomes measured included the incidence rate ratio (IRR) of discontinuation of the index AED; change in dose of index AED or addition of another AED; and the event rate ratio (ERR) of the composite of all-cause emergency department (ED) visits or hospitalisations. The key results suggested no differences for lamotrigine and divalproex in AED utilisation changes between the switchers and non-switchers (IRR for lamotrigine 1.00, 95% confidence interval (CI) 0.84-1.19; IRR for divalproex 1.02,

95% CI, 0.88-1.42). Compared with non-switchers, the phenytoin switch cohort had a greater incidence of AED utilization changes (IRR 1.85, 95% CI 1.50-2.29). The switch versus non switch cohorts did not demonstrate differences in ED visits or hospitalisations for the studied AEDs (ERR for phenytoin 0.96, 95% CI 0.80-1.16; ERR for lamotrigine 0.97, 95% CI 0.80-1.17; ERR for divalproex 0.83, 95% CI 0.66-1.06). Members noted that the authors concluded that brand to generic switching of phenytoin was not associated with more clinical events but was associated with increased index drug discontinuations, dose changes, and therapy augmentations. Members noted that Lamotrigine or divalproex brand to generic switching was not associated with increased incidence of events or utilisation changes compared with patients remaining on the branded product.

- 6.16 The Committee noted a prospective open-label study by Scherr et al (Psychiatric Services 1998;49:1355-1357) where the substitution of immediate-release valproic acid for divalproate sodium was evaluated in the treatment of 47 adult psychiatric inpatients who had been stabilized on divalproex for at least one month. Members noted that after two weeks, no significant change in Clinical Global Impressions scale (CGI) scores or in seizure frequency occurred, and serum valproate concentrations decreased by 14.4% (p=.001). One patient was restarted on divalproex because of gastrointestinal complaints. Among the 19 patients remaining hospitalised at six months, mean CGI scores did not significantly change.
- 6.17 The Committee noted an open clinical trial substitution study by Vadney and Krusher (Mental Retardation 1997;35:468-476) which considered the effects of switching valproate brands. This 8 week, open clinical trial substitution study, suggested that generic Valproic Acid USP may be successfully switched with brand-named Depakene Valproic Acid. 64 subjects with seizure disorders were randomly assigned to either brand-named Depakene or Generic Valproic Acid USP. Members noted that after 4 weeks they were switched to the other medication. Blood levels and seizures were monitored, and subjects had no statistically significant changes in seizures or blood levels when comparing the two treatment regimens.
- 6.18 The Committee noted that there were guidelines and position statements related to generic substitution of anti-epileptic drugs.
- 6.19 The Committee noted that Paesschen et al (Eur J Paediatric Neurology 2009;13:87-92) reviewed the potential challenges and issues related to the use of generic medication in epilepsy. Members noted that the authors advised that patients stay on the same formulation of the first AED, whether a brand name or generic AED and that switching AED formulations should always be done with the necessary caution and under the physician's supervision. Members note that the authors also suggest that closer follow-up during the transitional period is necessary, and dosage adjustment may be required and that the patient should be given full and correct advice about risks involved in switching AED formulations.
- 6.20 The Committee noted a Lancet Neurology commentary (Lancet Neurology 2010;9:227) which stated that generic substitution should be done with caution and that firm evidence of safety was not available.

- 6.21 The Committee noted that the American Academy of Neurology opposes generic substitution of AEDs and that the American Epilepsy Society requires patient and physician consent.
- 6.22 The Committee noted that the Neurology Subcommittee (2009) supported the use of generic when initiating therapy but that there was a need to keep the innovator brand for patients who are stabilised on it. Members noted that recent discussion related to another AED indicates concerns from neurologists about changing brands of AED due to the risk of breakthrough seizures and that they would be opposed to compulsory brand switching.
- 6.23 Members noted that it was unclear whether therapeutic drug monitoring was useful with sodium valproate except possibly for assessment of compliance.
- 6.24 Members considered that it may be difficult to convince patients of the safety of changing brands. Members considered that the possible anxiety related to switching might cause seizures, if for example this were to lead to loss of sleep and/or to hyperventilation. Members also noted the significant consequences of loss of seizure control on driving, and that a single seizure may prevent the patient from being eligible to drive for 12 months.
- 6.25 Members considered that listing as a sole supply would cause difficulties as this would result in all patients with epilepsy having to switch brands with every change of supplier. Members highlighted that the problem relates to switching brands of sodium valproate for patients with epilepsy, whether it be an innovator to generic switch, generic to innovator, or a generic to generic switch, as switching may be associated with loss of seizure control.
- 6.26 The Committee considered that a generic sodium valproate could be appropriate for those patients initiated on valproate therapy who were considered appropriate by their prescriber. The Committee also considered switching from the innovator brand to a generic sodium valproate might be suitable for non-epilepsy indications.
- 6.27 Members considered that there may be need for increase monitoring when brand switching as compared to dose changes associated with one brand.
- 6.28 The Committee considered that PHARMAC staff's estimation of the indications related to valproate patients to be half epilepsy and half other disorders to be reasonable.
- 6.29 The Committee considered that "sole supply" would have the advantage of not requiring further switching of formulation, but also noted that switching all patients with epilepsy to generics would not be desirable and may likely be opposed by clinicians and patient advocacy groups. The Committee considered that mandatory switching would not be appropriate. The Committee also highlighted its concern that if there was more than one brand/generic funded there would be a potential for switching of formulation without the patient or clinician knowing, which may pose a risk to patient safety with loss of seizure control, although this could be managed in part by listing the formulations as being not interchangeable in treatment of epilepsy. The committee was not opposed to listing a generic sodium valproate within this parameter.

- 6.30 The Committee noted that although the applicant has a syrup available, the availability of a 100mg crushable tablet dosage form would be desirable

7 Vitamin D for the prevention of and treatment for Vitamin D deficiency in pregnancy and infancy

Application

- 7.1 The Committee reviewed an application from the Ministry of Health requesting funding for daily vitamin D-only preparations for prophylaxis of rickets by administration to pregnant women and to infants, and for treatment of rickets in children.

Recommendation

- 7.2 The Committee **recommended** that the funding application for a daily vitamin D-only preparation for administration to pregnant women or infants to prevent rickets in infants be declined.
- 7.3 The Committee **recommended** that a daily vitamin D-only preparation for administration to pregnant women for prophylaxis of rickets in infants at high risk be listed in the Schedule if it is cost-neutral to Cal-d-Forte monthly tablets.
- 7.4 The Committee **recommended** that a daily vitamin D-only preparation for administration to infants for prophylaxis of rickets in infants at high risk of rickets be listed in the Schedule if it is cost-neutral to Vitadol C daily drops.
- 7.5 The Committee **recommended** that a vitamin D-only preparation for treatment of infants with rickets be listed in the Schedule with a low priority.
- 7.6 The Decision Criteria particularly relevant to these recommendations 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; and (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 7.7 The Committee noted the applicant's concern around vitamin D levels following new recommendations published in the Companion Statement on Vitamin D and Sun Exposure in Pregnancy and Infancy in NZ, advising that infants be kept out of direct sun "until mobile", which is about two years. The Committee considered that there is no evidence to help predict the impact this recommendation may have, such as the extent it will be adhered to or what population levels of vitamin D deficiency may result.

- 7.8 The Committee noted that two alternatives are already funded without restriction on the Schedule. Members noted that include here) Vitadol C contains 400 IU of vitamin D per 10 drops (0.3ml) , which is the same dose requested by the applicant. Vitadol C also contains 667 u of vitamin A and 33 mg of vitamin C per 10 drops (0.3ml). Members also noted the open funding for Cal-d-Forte, a 50,000 IU tablet that is used for monthly dosing in adults.
- 7.9 The Committee noted that, in the New Zealand registry, 50 cases of rickets have been reported over a recent two-year period (42 per 100,000 births). Members considered that the true rate was likely to be higher. Members noted that incidents of rickets occurred mostly among children belonging to Indian and other dark-skinned ethnic groups. Members noted an English study in which 93% of cases occurred in the resident Asian population (Zipitis Arch Dis Childhood 2006;91(12):1011-4).
- 7.10 The Committee considered evidence for the reduction of rickets by prophylaxis with vitamin D. The Committee considered that while there was evidence that supplementation with additional vitamin D increases vitamin D serum concentrations the evidence available was of low quality for determining health outcomes in patients. The evidence included a Cochrane review (De-Regil 2012. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008873) which assessed randomised controlled trials of vitamin D supplementation in pregnancy for gestational diabetes low birth weight pre eclampsia and preterm birth. Members considered that the quality of trials reviewed was low, with limitations such as few participants, missing data, and lack of ITT analysis. Members also highlighted that three of the trials used doses greater than the current preparation (ie greater than 50,000 IU). The review concluded that supplementation increases vitamin D levels in mothers but provided no indication that this results in health gains for the mother or in any of the outcomes assessed.
- 7.11 Members also noted a longitudinal study (Lawlor et al Lancet 2013;381: 2176-2183) that followed 3,960 mother-infant pairs. Members noted that this study found no association between maternal vitamin D status during pregnancy and later bone mineral content in offspring at mean age 9.9 years.
- 7.12 Members noted that there were no studies that assessed the effect of supplementation on subsequent bone density and rickets in children, but the Cochrane review noted that a study is currently in progress in New Zealand (Grant C unpublished) which was examining this.
- 7.13 The Committee noted that there was no evidence to support mass supplementation of vitamin D for all pregnant and breast fed infants in the NZ population. The Committee noted a randomised controlled trial of supplementation among 132 infants in Canada of three doses of daily Vitamin D supplementation (Gallo et al. JAMA 2013;17:1785-92) This trial reported that a dose of 400IU daily achieved concentrations of 75 nmol/l or greater in 55% of infants at 3 months, while to achieve this level in 97% of infants at 3 months required a dosage level that increased levels in some infants to those that have been associated with hypercalcaemia. There was no dose-response relationship observed between bone mineral density and Vitamin D. The Committee was not aware of any studies assessing the long term benefits and harms of population level supplementation.

- 7.14 The Committee compared vitamin D-only drops with the already-funded Vitadol C. Members noted the applicant's assertion that, due to its high vitamin A content, Vitadol C is not suitable for treating vitamin D deficiency in infants as it could lead to a vitamin A overdose. However, members considered that the applicant had not provided any evidence in support of this claim. Members considered that a safe dose of Vitadol C could be provided without exceeding recommendations for upper limits in this age group. (Australian National Health and Medical Research Council and the New Zealand Ministry of Health, 2006
<http://www.nhmrc.gov.au/guidelines/publications/n35-n36-n37>)
- 7.15 The Committee compared daily vitamin D-only drops with the already funded monthly cholecalciferol 50,000 IU tablets (Cal-d-Forte) during pregnancy. The Committee noted the applicant's assertion that daily dosing would be safer than a monthly dose. The Committee considered that no evidence had been presented to suggest that monthly dosing was unsafe in pregnant women. Members also highlighted a potential benefit for compliance with a monthly dose versus a daily dose.
- 7.16 Members discussed factors that might lead an infant to be at high risk of rickets. Members noted risk factors such as dark skin or being born in the winter months, or if the mother has low vitamin D levels (eg wears a veil or otherwise has reduced sun exposure during pregnancy).
- 7.17 The Committee considered that Vitadol C is an appropriate product for prophylaxis during pregnancy and infancy, and that the resulting dose of vitamin A was not high enough to cause concern at the recommended daily dose. The Committee also considered that Cal-d-Forte was appropriate to increase vitamin D levels during pregnancy. Members considered that were a vitamin D-only product be listed, it would also be an appropriate product for the purpose. However, members considered that, since Vitadol C and Cal-d-Forte were already open listed on the Pharmaceutical Schedule, it was unclear how funding a vitamin D-only preparation would address the problems that existing products have not addressed.
- 7.18 The Committee noted several published case reports of hypercalcemia during treatment of rickets with pharmacologic doses of Vitamin D (Vanstone et al Paediatrics 2012;129:1060-1063) as well as reports from a local paediatrician of cases of hypercalcemia even with gentle application of the 50,000IU preparation. The Committee considered that the availability of a daily dose alternative, where higher doses are required in treatment of rickets, would be helpful in this situation.

8 Rotavirus vaccine

Application

- 8.1 The Committee reviewed an application for the funding of universal rotavirus vaccination.

Recommendation

- 8.2 The Committee **recommended** that a rotavirus vaccine be funded with a medium priority for universal childhood vaccination.
- 8.3 The Decision Criteria particularly relevant to these recommendations 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; and (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

- 8.4 The Committee had previously noted the minutes from the March 2013 Immunisation Subcommittee of PTAC meeting regarding rotavirus with the recommendation that rotavirus vaccination for infants aged under 15 weeks of age and no vaccination being administered to children aged 8 months or over be funded with high priority.
- 8.5 Committee noted that rotaviruses are non-enveloped RNA viruses that are classified according to the two surface proteins they contain: VP7, the 'G' glycoprotein, and VP4, the protease-cleaved 'P' protein. The G and P proteins are targets for the neutralising antibodies that contribute to protection against reinfection and disease. A binary typing system, consisting of both P and G types, has been developed. Rotavirus strains are most commonly referred to by their G serotype, with G1, G2, G3, G4 and G9 accounting for around 90% of serotypes. The most common P types found in combination with these G types are P1A[8] (found with all common G types except G2) and P1B[4], usually found in combination with G2. In New Zealand (NZ) G1 is the most commonly detected strain (54-65%) with the majority of these being P[8]G1.
- 8.6 The Committee noted Rotavirus infects almost all children by age 5 years. Transmission occurs through the faecal-oral route both through close personal contact and fomites. The clinical illness experience ranges from mild illness to frequent large volume diarrhoea and vomiting, dehydration and electrolyte disturbance. Up to a third of children will develop a fever greater than 39°C. The illness lasts from 3-8 days and children are infectious until approximately 8 days after the onset of symptoms.
- 8.7 The Committee noted that some protection for new born infants may be provided by breast feeding and maternal transmission of antibodies. Death is rare in developed countries like NZ. However the Committee did note one recent case, and estimated a rate of approximately one death per year.
- 8.8 The Committee outlined that current treatment is supportive, with isolation from childcare centres, oral rehydration or rapid rehydration in hospital via nasogastric tube or intravenous infusion.
- 8.9 The Committee considered that rates of rotavirus illness in developed and developing countries are similar. This indicated that good hygiene and clean water supplies are unlikely to have significant effects on disease prevention. Immunisation therefore presents an important public health measure to reduce rotavirus disease burden.

- 8.10 The Committee noted the results of Craig et al (NZ Child and Youth Epidemiology Service 2012). This study showed that children in the lowest two deciles (NZ deprivation 9 to 10) were 2.02 (95% CI 1.94-2.10) times more likely to be admitted with gastroenteritis than children in the highest two deciles (NZ deprivation 1 to 2). This study also showed that for the same period, Pacific children were 1.46 (95% CI 1.41-1.51) times more likely than non-Pacific children to be admitted to hospital.
- 8.11 The Committee noted that from 2002-2008 on average one child per year died from complication associated with gastroenteritis.
- 8.12 The Committee noted that for the period 2005 to 2009 gastroenteritis was the second highest cause of potentially avoidable hospital admissions in New Zealand (Craig et al NZ Med. J 2012;125(1366):38-50).
- 8.13 The Committee noted a study by Grimwood et al. (J Paediatr Child Health 2006;42:196-2-3). This report studied children hospitalised to 8 NZ hospitals with a coded diagnosis of gastroenteritis between 1 May 1998 and 30 April 2000. Of 2,019 enrolled children 56.4% provided stools for testing and of those 42.6% were rotavirus positive. Rotavirus detection varied significantly according to age (26.8% for 0-5 months, 42.5% 6-11 months, 52.5% 12-35 months; $p < 0.001$) and by season (51.2% winter/spring, 24.5% summer/autumn, $p < 0.001$). Rotavirus-positive children were more likely to be dehydrated (50.6% vs 37.4%; $p < 0.001$) than children with other acute gastroenteritis. Median hospital stay was similar 1 vs 2 days ($p = 0.09$).
- 8.14 Based on the results of Grimwood et al, the Committee considered the estimated national hospitalisation rate for rotavirus gastroenteritis for children aged less than 3yrs to be 634 per 100,000 person-years, with rotavirus infections resulting in 1 in 52 children being hospitalised by 3 years of age. However the Committee noted a number of limitations with that analysis, in particular only large urban hospitals were included (57% of gastroenteritis hospitalisations according to NZHIS data over this period), just over half of the hospitalised children submitted stool samples for testing, and there was variation between study sites in numbers of children being tested (range from 20% to 94%). Further the Committee noted known limitations with ELISA testing, which fails to detect approximately 10% of true positive cases. As such the Committee considered the estimate of hospitalisations to be plausible, but potentially low.
- 8.15 The Committee considered the impact of introducing a new vaccine onto the Immunisation Schedule.
- 8.16 Members noted the Ministry of Health reported uptake for childhood vaccination in New Zealand, which indicated that 92% of 2 year olds were fully vaccinated, 4.6% declined to be vaccinated and 0.6% had opted-off the immunisation register. Vaccination uptake was similar by socioeconomic deprivation but the particularly high rates of completed vaccination for Pacific infants (most at risk from rotavirus gastroenteritis) should be noted.
- 8.17 Members noted some concern of patients in relation to immune system burden, and timing of vaccination with the existing immunisation regime. Overall the Committee considered that both of the rotavirus vaccines would be able to fit within the existing vaccination schedule without undue difficulty.

- 8.18 The Committee considered the results of the key relevant trials of each of the two vaccines and a Cochrane review.
- 8.19 The Committee noted the results of the REST study (Vesicari et al. NEJM 2006;354(1):23-33). This study was a double-blind (with sponsor blinding), placebo-controlled, randomised phase III trial conducted during 2001-2004 in 11 countries (North, Central, South America and Europe). 70,301 infants were enrolled, including 34,035 who received the RotaTeq vaccine and 34,003 received a placebo. 98% received at least one dose, 85% received three doses and were followed by active surveillance for 42 days after the third dose. 81% were followed for 1 year after the first dose.
- 8.20 The Committee considered that the study was sufficiently powered to evaluate intussusception risk given the association between an earlier oral vaccine (Rotashield, withdrawn in 1999) and increased rates of intussusception. There was no increased risk of intussusception in vaccine recipients within the 42 day period after any dose (6 vaccine recipients, 5 placebo, relative risk (RR) 1.6; 95% CI 0.4-6.4). RotaTeq was reported to be well tolerated, and the incidence of fever, vomiting, diarrhoea and blood in stools was similar between vaccination and placebo recipients during the 42 day safety monitoring period.
- 8.21 The Committee also noted that the study looked at the efficacy of the vaccine in reducing hospitalisations or ED care for RV gastroenteritis. Nested substudies evaluated safety, immunogenicity and efficacy against less severe rotavirus gastroenteritis. Sites for sub-studies were prospectively identified. Approximately 28,000 subjects in the vaccine and placebo groups respectively were included in the per protocol analysis of use of healthcare resources:
- visits to the ER: 13 vaccinated, 191 placebo subjects (93% reduction (95% CI 89-97%))
 - hospitalisation: 6 vaccinated, 138 placebo subjects (96% reduction (CI 91-98%))
 - lost work days of parents: 65 vaccinated, 487 placebo (87% reduction (CI 78-92%))
- 8.22 The Committee noted the results of the Rotarix trial by Ruiz-Palacios et al. (NEJM 2006;354(1):11-22). The study was a double-blind, placebo-controlled, randomised phase III trial conducted during 2003-2004 in 11 South American countries and Finland. 63,225 infants were enrolled in the safety study including 31,673 who received the vaccine and 31,552 received placebo. Participants were followed for 100 days.
- 8.23 In Ruiz-Palacios et al, 20,169 infants were enrolled in the efficacy study, 10,159 to the vaccine group and 10,010 to the placebo groups. Participants were followed until they were 1 year of age. The proportions of infants who were withdrawn from the study and the reasons for withdrawal were similar.
- 8.24 Safety end points were risk of intussusception within 31 days of administration of the vaccine and serious adverse events during the study period. The primary efficacy endpoint was prevention of severe RV gastroenteritis according to the case definition

from 2 weeks after dose 2 to 1 year of age. Secondary efficacy endpoints were severe RV gastroenteritis according to a severity scale (Vesikari Scale), severe gastroenteritis from any cause, severe RV gastroenteritis after the first dose of vaccine and whether RV1 offered protection against different circulating strains in infants up to 1yr of age.

8.25 The Committee considered that the study was sufficiently powered to evaluate intussusception risk. Like the RotaTaq study they did not describe how subjects were randomised. There was no discussion on sponsor-blinding and exclusion criteria were not discussed in the paper. Furthermore this study contained infants from developing countries with differing health systems and access to oral rehydration solution so transferability to NZ context may be an issue in interpreting the results of this study.

8.26 The Committee noted that the study defined severe gastroenteritis (GE) as diarrhoea requiring overnight hospitalisation or oral/ iv rehydration in a medical facility. The severity of GE was quantified using a 0-20 severity scale (Vesikari scale). 11/20 or greater was considered severe. Members also noted the following outcomes from the study:

- a) There was no increased risk of intussusception in vaccine recipients within the 31 day period after any dose – 6 vaccine recipients 7 placebo (RR 0.85; p=0.78). Also, there were significantly fewer (mainly gastroenteritis-related) adverse events reported in the vaccine group vs placebo group (293/10,000 infants vs 331.8/10,000 infants, p=0.005);
- b) Vaccine recipients had significantly lower hospitalisation incidence than placebo: 9 for the vaccine group, 59 placebo (279.7 vs 317.9/10,000 infants, p=0.005);
- c) Vaccine recipients had significantly lower incidence of severe RV gastroenteritis according to clinical definition than placebo (12 vs 77, ie. 2 vs 13.3 infants with at least one episode/1000 infant years, p<0.001). Vaccine efficacy was calculated as 84.7% (95% CI 71.7-92.4%) against severe rotavirus gastroenteritis from 2 weeks after dose 2 until 1yr of age, and 81.1% for infants who only received 1 dose (68.4-95.3%);
- d) Vaccine recipients were less likely to get severe diarrhoea as scored by the Vesikari Scale (score >14: 7 vaccine vs 54 placebo; score >18: 0 vaccinated cases vs 16 placebo);
- e) Vaccine efficacy against RV strain G1P(8) was 90.8% and slightly lower (87.3%) against strains sharing only the P(8) antigen;
- f) Vaccine efficacy against severe GE from any cause was 40% (28-50%), indicating perhaps that the presence of false negative rotavirus antigen tests.

8.27 The Committee noted the results of the Cochrane Review (Cochrane Database of Systematic Reviews 2012;2:CD008521). The Committee noted that the review assessed 43 RCTs covering a total of 190,551 children. Of these, 31 trials assessed RV1 and 12 trials assessed RV5. The Committee noted the following:

- There was no compelling evidence that either vaccine is better in efficacy or safety at the present time;
- Both vaccines prevented over 80% rotavirus gastroenteritis causing hospitalisation in children aged less than 1 year;
- Rotarix prevented 80% of hospitalisations (95% CI 65%-89%) in 7 trials of moderate-quality evidence with 35,005 participants and 70% of all rotavirus diarrhoea (95%CI 50%-82%) in seven moderate quality trials with 12,130 participants. In children aged 1-2 years these reductions were 84% (95% CI 79%-88%) in eight moderate quality trials with 32,854 participants; and 70% (CI 57%-79%) six trials of moderate quality with 8041 participants;
- Neither vaccine demonstrated statistically significant differences in incidence of intussusception in pooled analysis;
- RV1: Pooled results showed no increase in risk for intussusception for those receiving the vaccine (27 cases/53,887 vaccine vs. 23/44,560 placebo).

8.28 The Committee noted that the World Health Organization (WHO), the NZ Paediatric Society, the Immunisation Technical Forum and the Immunisation Subcommittee of PTAC have recommended universal vaccination for Rotavirus. The Committee noted the National health Committee paper which recommended not funding a universal rotavirus vaccination in New Zealand as it was not cost effective against the National Health Committee decision criteria. Members noted that Australia has immunised against rotavirus since 2007 and that the United Kingdom would begin universal vaccination in September 2013, having initially rejected it on the grounds of poor cost-effectiveness.

8.29 The Committee considered a targeted programme as an alternative to universal vaccination in the event that this was considered more cost effective. The Committee considered that universal vaccination was preferred, and that targeting had limited evidence. Members noted that targeting was theoretically possible if necessary. Targeting to high risk infants such as preterm infants, low birth weight or comorbidities may increase savings attributable to preventing the costs of illness. The Committee noted the costs to society of rotavirus disease, with the highest incidence of hospitalisation for childhood gastroenteritis occurring in those groups with the greatest socioeconomic deprivation. The Committee noted the issue of herd immunity and waning of vaccine effect, which PHARMAC staff had raised relating to cost effectiveness modelling. The Committee considered that there was limited evidence for either. However, the Committee considered that the evidence on balance pointed toward a possible herd immunity benefit. The Committee therefore recommended PHARMAC exclude any waning of vaccine effect or herd immunity in its economic model. Members considered that in practice the disease in older people was less severe, so waning of effect was less of an issue. Regarding herd immunity, the Committee considered that data suggested a vaccination programme rendered contracting the illness less likely. Specifically, data post-introduction of rotavirus vaccine in the U.S.A and Australia has been associated with reductions in rotavirus gastroenteritis in all age groups, not just the vaccinated, suggesting possible herd immunity.

9 Varicella vaccine

Application

- 9.1 The Committee considered an application generated by PHARMAC for the listing of varicella vaccine in Part II of Section H and Section I of the Pharmaceutical Schedule.

Recommendations

- 9.2 The Committee **recommended** that the application for universal varicella vaccination be declined.
- 9.3 The Committee **recommended** that varicella vaccination be funded for high risk patients with a high priority.

The Decision Criteria particularly relevant to these recommendations 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; and (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

- 9.4 The Committee had previously noted the minutes from the March 2013 Immunisation Subcommittee of PTAC meeting regarding varicella with the recommendation that varicella vaccination for all eligible patients be funded with a high priority.
- 9.5 The Committee noted the minutes from the March 2013 Immunisation Subcommittee of PTAC meeting regarding universal varicella vaccination with the recommendation that varicella vaccination for infants be funded with a high priority.
- 9.6 The Committee noted the Ministry of Health antigen review 2012 on varicella vaccination. The Committee noted the National Health Committee review of varicella vaccine and its recommendation against universal vaccination.
- 9.7 The Committee noted the United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) statement which did not recommend a universal varicella vaccination for children in light of a high probability of it not being cost effective.
- 9.8 The Committee noted that varicella-zoster virus causes two distinct diseases: varicella (chicken pox) and herpes zoster (shingles). Members noted that varicella is a highly contagious disease transmitted by the airborne route. Following primary infection the virus establishes a lifelong latent infection in the root ganglia and can subsequently reactivate to cause zoster. The virus can be transmitted from patients with zoster and cause varicella in those not immune, however it is less contagious than varicella and likely to require direct contact with lesions.

- 9.9 The Committee noted that varicella infection is an almost universal childhood disease and in most cases is relatively benign; however it can cause serious complications. Members noted that complications were more common in adult cases, with up to five times the incidence of hospitalisation compared with children (Halloran et al. *Am J Epid* 1994;140:81-104). Members noted that patients who were immunocompromised also had a higher rate of serious complications.
- 9.10 Members noted that herpes zoster, caused by reactivation of the varicella virus, can result in long term morbidity. The Hope-Simpson hypothesis (*Proc R Soc Med.* 1965;58:9-20) suggests that on-going exposure to varicella virus in the community is protective against the development of herpes zoster.
- 9.11 The Committee noted the 2008 review of cost effectiveness analyses of varicella vaccination (Rozenbaum et al. *Expert Rev. Vaccines* 2008;7:753-782). The authors identified 22 studies, with 2 including modelling of a potential increase in herpes zoster incidence. Of the studies that used a dynamic model and included the impact of herd immunity and vaccine waning, the results were mixed as to whether an infant vaccination program would be cost effective from a healthcare perspective. The Brisson et al study (*Vaccine.* 2010;28:3385-97) incorporated these aspects and a potential effect on herpes zoster incidence indicated a poor benefit to cost ratio.
- 9.12 The Committee noted the cost effectiveness model of varicella and combined varicella and herpes zoster vaccination programmes in the United Kingdom by van Hoek et al (*Vaccine* 2012;30:1225-1234). Members noted that the results were sensitive to the time-frame of the analysis; in the 30-50 year period following initiation of a vaccination programme the vaccination would not be cost effective. After this period, when the vaccinated cohorts pass into the age groups when they are at greatest risk of developing herpes zoster, the analysis became more favourable. Members noted that the favourable cost-effectiveness assumed that those patients who responded to varicella vaccination would be less likely to develop herpes zoster at older ages than those naturally infected; however this assumption had a weak evidence base.
- 9.13 The Committee noted a paper examining varicella incidence between 1995 and 2005 in two active surveillance sites in the United States (Guris et al. *J Infect Dis.* 2008;197(Supplement 2):S71-S75). A single dose of varicella vaccine was given to children aged 12 to 18 months and to designated high risk groups from 1995 onwards. The age specific incidence of varicella for all age groups reduced significantly (57% reduction in adults and 90% in children aged 1 to 9 years). Members noted that a shift in the median age of varicella was observed. The benefit of herd immunity was noted, with a sustained decline in incidence in infants (ineligible for vaccination) and adults where the rate of vaccination appeared to be low. The authors had noted that 'without implementation of catch-up vaccination and administration of the second dose of varicella vaccine, in low-incidence areas there is likely to be accumulation of susceptible children and young adults, which has implications for the future. Numbers of unvaccinated persons, as well as 15%-20% of vaccinated persons who are completely or partially susceptible to varicella, may accumulate rapidly. In the future, outbreaks might be reported in age groups even older than we see today.' The Committee also noted the above vaccine programme-related prevalent 15-20% susceptibility to varicella in adults (aged 20 years and over) contrasted with less than 2% of adults being susceptible in the pre-vaccine era.

- 9.14 The Committee noted the Kuter et al paper (Ped Infect Dis J. 2004;23:132-137), a multicentre trial involving children with a mean age of 4.4 years, randomised to receiving either one or two doses of varicella vaccine. 2,216 children participated in the study. The administration of one vaccine resulted in significant amelioration of varicella disease; receiving a two dose regime significantly decreased the rate of varicella illness breakthrough and increased vaccine efficacy. Both regimes were 100% efficacious against severe varicella. Members noted that only children who were initially seronegative and seroconverted around 6 weeks after completion of the vaccine regime were eligible for serologic follow up. Members noted that this appeared to be approximately 80% of the one dose cohort and 70% of the two dose cohort. Members noted that there was a high dropout rate and it was unclear how this was taken into account in the results. Members noted that the antibody persistence rate was close to 100% throughout the 9 year follow up for both arms. The authors noted that the exact role played by exogenous vs. endogenous boosting in the persistence of varicella antibody in this population cannot be clearly established.
- 9.15 The Committee noted the Brisson et al paper (Vaccine 2010;28:3385–3397) which modelled the impact of one and two dose varicella vaccination on the epidemiology of varicella and herpes zoster. Following the start of a one dose vaccination programme (with catch up in 5 and 9 year olds) the model predicted an immediate steep decline in varicella cases, which would last for more than 10 years. During this 10 year period, susceptibles (comprising of primary failures and unvaccinated individuals) would slowly accumulate and once a threshold of susceptible individuals was reached a varicella epidemic would occur. Afterwards the epidemic the infection would settle into a new equilibrium, with 40% lower numbers of infections than before the introduction of varicella vaccination. The model predicted that the mean age of infection would increase over time and at 80 years post vaccination the mean ages for natural and breakthrough cases of varicella occurring would be about 20 and 40 years of age respectively. The results were similar for vaccine coverage scenarios of between 70% and 95%. The model predicted that the main benefit of a two dose programme would be in reducing varicella breakthrough; however in the short to medium term an increase in herpes zoster incidence was predicted to be slightly higher as there would be a greater efficacy in preventing varicella.
- 9.16 The Committee noted a paper by Poletti et al (PLoS One 2013;8) which modelled the impact on herpes zoster incidence following introduction of a varicella vaccination programme in three European countries. The model concluded that following varicella immunisation an increase in herpes zoster incidence would not be a certainty, but would depend on the presence or absence of factors promoting a strong boosting intensity and which might or might not be heavily affected by changes in varicella circulation due to mass immunisation. An increase in herpes zoster was predicted to occur in countries where the pre-vaccination incidence rate of herpes zoster was lower, possibly due to a higher force of boosting, whereas the increase in herpes zoster incidence would be minor or absent where the force of boosting was milder. Members considered that it would be difficult to transfer the model to the New Zealand setting; however as New Zealand had a high incidence of chickenpox it would be likely that the force of boosting would be high. The model further predicted that following a mass vaccination programme the proportion of varicella cases occurring in older individuals would increase markedly.

9.17 The Committee considered that the evidence for varicella vaccination to prevent infection and complications in vaccinated individuals was strong, however the studies were undertaken in a background of wild type varicella vaccination that may have a boosting effect that could potentially confound the results. The Committee noted limited or conflicting evidence for the durability of long term vaccine response, greater than 10 years, and the effect on herpes zoster morbidity in the community.

9.18 The Committee considered that varicella vaccine would provide herd immunity and this would provide a significant benefit to those most at risk of varicella infection – the very young and immunocompromised. Members considered the high risk groups identified by the Immunisation Subcommittee would benefit most from a targeted varicella vaccination programme.

9.19 The Committee considered that the risks from a universal varicella vaccination programme, i.e. later age of varicella infection in susceptible individuals and a potential increase in herpes zoster in the elderly, would outweigh the benefit of reduction in varicella infection for otherwise healthy individuals. Members considered that the evidence for the effect of varicella vaccination on herpes zoster and age of infection would develop over time. Members noted that a herpes zoster vaccine was registered in New Zealand and an application for this product should be considered as part of the varicella discussion.

9.20 The Committee recommended funding varicella vaccination to prevent transmission to high risk individuals with a high priority. Members recommended that the following restriction be applied to funded varicella vaccination:

- 1 For varicella non-immune patients
 - 1.1 with chronic liver disease who may in future be candidates for transplantation; or
 - 1.2 with deteriorating renal function before transplantation; or
 - 1.3 prior to solid organ transplant; or
 - 1.4 prior to any elective immunosuppression*; or
 - 1.5 for post exposure prophylaxis who are immune competent inpatients (inpatient only).
- 2 For patients at least 2 years after bone marrow transplantation, on advice of their relevant specialist;
- 3 For patients at least 6 months after completion of chemotherapy, on advice of their relevant specialist;
- 4 For HIV positive non immune to varicella with mild or moderate immunosuppression on advice of HIV specialist;
- 5 For household contacts of paediatric patients who are immunocompromised, or undergoing a procedure leading to immune compromise where the household contact has:
 - a) adult household contact – a negative serology result for varicella; or
 - b) child household contact – no clinical history of varicella or negative varicella serology

* immunosuppression due to steroid or other immunosuppressive therapy must be for a treatment period of greater than 28 days

9.21 The Committee **recommended** declining a universal childhood varicella vaccination programme.

10 Human Papillomavirus Vaccine (HPV) for males

Application

10.1 The Committee reviewed an application for the HPV vaccine in males aged between 9 and 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16 and 18.

Recommendation

10.2 The Committee **recommended** that the HPV vaccine be available to all males aged 11-19 years of age be listed in the Pharmaceutical Schedule with a low priority.

10.3 The Committee **recommended** that the HPV vaccine for males aged between 9 and 26 years who self-identify as having sex with other males be listed in the Pharmaceutical Schedule with a high priority.

10.4 The Committee **recommended** that access in the Pharmaceutical Schedule to HPV vaccine for females be amended so they may receive the vaccine from 11 years rather than 12 years with a high priority.

10.5 The Decision Criteria particularly relevant to these recommendations 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; and (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

10.6 The Committee had previously noted the minutes from the March 2013 Immunisation Subcommittee of PTAC meeting regarding HPV with the recommendation that HPV vaccination for males aged between 11 and 18 be funded with a low priority; the age HPV vaccination for females be lowered to 11 years with medium priority and access be widened for males who have sex with males with high priority.

10.7 The Committee noted that the HPV vaccine is indicated for women aged 9 to 45 years of age for the prevention of cervical, vulva, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts and infection caused by HPV types 6, 11, 16 and 18; and in males aged 9 to 26 years for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16 and 18.

10.8 The Committee noted that a quadrivalent vaccine (Gardasil) is currently funded for girls aged 12 (in Year 8 at school) via three scheduled doses at school over a period of 6 months, or for females under 19 years through general practice through a catch up programme. The Committee noted that currently uptake is approximately 50%.

- 10.9 The Committee considered the previous Immunisation Subcommittee recommendation to amend the age of eligibility of the vaccine for girls from 12 to 11 years. The Committee considered there was some evidence to suggest that the vaccine was more effective if given at an earlier age but it was uncertain as to how long immunity lasts. The Committee also noted it unlikely there would be any additional adverse effects and there would be no additional costs after a two year period. The Committee considered that uptake may increase as a result of this change.
- 10.10 The Committee considered that all males are at risk from HPV infection and that these may not be reduced significantly by use of condoms. Based on epidemiological modelling (Kim J, Goldie S. *BMJ* 2009;339:b3884), the Committee considered that the herd immunity impact from immunising females would start to provide significant benefits for males when approximately 80% females were vaccinated. The Committee considered that if boys were vaccinated with the HPV vaccine there would be herd immunity for females who did not receive the HPV vaccine. The Committee noted that males who have sex with males (MSM) are a high risk group, who are more likely to acquire HPV when compared with other males. The Committee noted that there is little herd immunity benefit in this group from vaccinating females.
- 10.11 The Committee noted that if there was a 100% uptake in women then this would not translate to 100% of men, given that a small proportion of men were exclusively males who had sex with males. The Committee noted if uptake could be increased to approximately 80% in females then there would be little benefit in vaccinating all men (apart from MSM) at all. The Committee noted that Australian vaccination rates in females were now greater than 80% but questioned if this rate of coverage could be achieved across all groups with the current strategies in New Zealand.
- 10.12 The Committee noted two high quality reviews; the 2012 Antigen Review for the New Zealand Ministry of Health and the European Centre for Disease Prevention and Control 2012 update. These both indicated evidence of effectiveness in boys.
- 10.13 The Committee noted that there was also strong evidence that the HPV vaccine was effective for boys and men (Giuliano et al. *N Engl J Med.* 2011;364:401-11). This randomised, placebo-controlled, double blind study enrolled 4,065 boys aged between 16 and 26 years from 18 countries. The boys were allocated in a 1:1 ratio to receive either the HPV vaccine or placebo. 3,463 reported their sexual partners were exclusively female and 602 reported they had sex with a male in the previous year. The Committee noted that, using an intention-to-treat analysis, 36 external genital lesions occurred in the vaccinated group compared with 89 in the placebo vaccination group, with a reported relative risk reduction of 60%. The Committee noted that in the per protocol analysis there were 6 genital lesions in the vaccinated group compared with 36 in the placebo group, resulting in an efficacy of 84%
- 10.14 The Committee noted that the vaccine would be more efficacious if it was given before the first sexual exposure and that the current evidence in men who have sex with men was limited to those with up to five male partners.
- 10.15 The Committee noted the subgroup analysis of the 602 males who have sex with males by Pelefsky et al (Pelefsky et al. *N Engl J Med.* 2011;365:1576-85.). The Committee noted that this paper reported vaccine effect against anal intraepithelial neoplasia. Using intention-to-treat analysis, efficacy rated was reported as 50%. The Committee

noted that due to the small number of events there was insufficient power to detect a significant impact on anal and oropharyngeal cancer

- 10.16 The Committee noted the cost-effectiveness analysis on the strategy of including boys in a HPV vaccination programme in the United States (Kim & Goldie BMJ 2009, cited above). The Committee noted that the cost-effectiveness of vaccinating boys as well as girls was modelled to exceed the threshold of value for money in the US, costing approximately US \$100,000 per QALY.
- 10.17 The Committee noted a paper comparing numerous cost-effectiveness studies regarding the HPV vaccination in developed countries (Brisson et al. Public Health Genomics 2009;12:343-351). The results of these studies suggest that the HPV vaccination is effective and cost-effective for girls; however whilst it is effective for boys it is not cost-effective for that group. The Committee noted that if coverage uptake for girls was approximately 80% then the cost-effectiveness of vaccinating boys is poor, as the boys already receive benefit from herd immunity.
- 10.18 The Committee noted that the cost-effectiveness of these vaccines were sensitive to both the cost of the vaccine and duration of vaccine effectiveness. The Committee noted that in the best case scenarios the cost-effectiveness was approximately US \$75,000 per QALY and often US \$200,000 per QALY. However, the Committee noted that the cost of the vaccine is higher in the US compared with New Zealand.