

PTAC meeting held 13 & 14 February 2014

(minutes for web publishing)

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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.

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

- (i) enable PHARMAC to carry out, without prejudice or disadvantage, commercial activities (section 9(2)(i)); and/or
- (ii) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j));

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting 13 & 14 February 2014

1. Matters Arising

Benzbromarone

- 1.1. The Committee noted correspondence from TeArai BioFarma relating to the funding of benzbromarone in gout patients with renal impairment and requesting that the Special Authority criteria be amended.
- 1.2. The Committee noted that benzbromarone was funded for patients subject to Special Authority criteria including a requirement for creatinine clearance ≥ 20 ml/min. The Committee noted that it had initially recommended funding for patients with a creatinine clearance ≥ 30 ml/min on the basis of efficacy rather than safety, however, this had been amended to ≥ 20 ml/min following review and recommendation by its expert Rheumatology Subcommittee.
- 1.3. The Committee considered that there was sufficient evidence to support the funding of benzbromarone in patients with a creatinine clearance ≥ 20 ml/min and < 30 ml/min. In particular members noted that the 2007 British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout recommends benzbromarone be used in patients with a creatinine clearance ≥ 20 ml/min and < 30 ml/min (Rheumatology (Oxford). 2007; 46: 1372-4.]. The Committee **recommended** that the Special Authority criteria for benzbromarone remain unchanged.

2. Subcommittee Minutes

Haematology Subcommittee – 22 November 2013

- 2.1. The Committee noted and accepted items 1 to 9 of the minutes, with the exception of recommendations in relation to tinzaparin (items 1.7 and 6), apixaban (items 1.8, 1.9 and 7) and rivaroxaban (items 1.10, 1.11, 1.12 and 8).
- 2.2. The Committee noted that tinzaparin would be considered separately by the Committee at this meeting.
- 2.3. The Committee deferred making a recommendation on apixaban and rivaroxaban for the various indications applied for. The Committee requested that the funding applications for both products be reviewed at its May 2014 meeting.

Neurological Subcommittee – 20 September 2013

- 2.4. The Committee noted and accepted items 1, 3, 4, 8 and 9 of the minutes.
- 2.5. The Committee considered the minute regarding multiple sclerosis treatments, with the consequent recommendations and treatment algorithm, provided by the Neurological Subcommittee at its September 2013 meeting.

Recommendations

- 2.6. The Committee **recommended** that natalizumab and fingolimod be funded as first-line agents for the treatment of Clinically Definite Relapsing Remitting Multiple Sclerosis (RRMS) for patients with Expanded Disability Status Scale (EDSS) scores 0 – 4, for the disability progression criterion of the entry criteria, with a medium priority.
- 2.7. The Committee **recommended** that interferon beta and glatiramer acetate not be funded as second-line agents, and that they should only be funded, for patients with Clinically Definite RRMS and an EDSS score 0 – 4 if treatment with both of the above recommended first-line agents (natalizumab and fingolimod) is not tolerated or is contraindicated, rather than funded for disease progression.

- 2.8. The Committee **recommended** that funding for treatment with natalizumab, fingolimod, an interferon or glatiramer acetate for clinically isolated syndrome fulfilling the McDonald 2010 diagnostic criteria for MS be declined, but noted that the Committee would review this recommendation should new evidence become available.
- 2.9. The Committee considered the proposed treatment algorithm by the Neurological Subcommittee and **recommended** that treatment stop should a patient's EDSS score progress by any of the following steps: 0 to 3.0, 1.0 to 3.0, 1.5 to 3.5, 2.0 to 4.0, 2.5 to 4.5, 3.0 to 4.5, 3.5 to 4.5, or 4.0 to 4.5.
- 2.10. With regards to the Stopping criteria proposed by the Neurological Subcommittee at its September 2013 meeting for all MS treatments, the Committee agreed with the Subcommittee's recommendation that if a relapse results in an increased EDSS score that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months be allowed from the start of the relapse in order for recovery to occur.
- 2.11. The Committee **recommended** that switching between natalizumab and fingolimod be permitted provided the stopping criteria are not met.
- 2.12. The Committee **recommended** that switching to or between interferon or glatiramer acetate be permitted only if natalizumab and fingolimod are not tolerated or are contraindicated, providing the stopping criteria are not met.
- 2.13. The Decision Criteria particularly relevant to this recommendation are: i) The health needs of all eligible people within New Zealand; (ii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iii) The clinical benefits and risks of pharmaceuticals; (iv) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; 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

Multiple sclerosis treatments

- 2.14. The Committee considered paragraphs 2.5, 2.11-2.13 and 2.20 of the Neurological Subcommittee's minutes and reiterated its previous view that the newer multiple sclerosis (MS) treatments appear to have better evidence of effectiveness. The Committee noted the conflicting evidence for effectiveness of the currently funded treatments for MS, which the Committee considered to be poor, and stated that it still considers at this time there is no evidence to support the use of the currently funded treatments as second-line agents if a patient continues to relapse or there is progressive disability.
- 2.15. The Committee noted the relatively poor cost effectiveness for the currently funded agents (beta interferons and glatiramer acetate) in the treatment of MS. The Members were mindful of better effectiveness of current treatments over the currently funded treatment and also the high costs of new therapies. Members considered that these treatments should be targeted to the patients likely to benefit most from such treatments.
- 2.16. The Committee considered that should new MS treatments be funded, the currently funded treatments could potentially be delisted from the Pharmaceutical Schedule. However, members also considered that the currently funded treatments may still have a place in the treatment of MS for those patients who are unable to tolerate the newer agents or for whom the newer agents are contraindicated.
- 2.17. Members considered that patients who are taking the currently funded treatments may need to be 'grandparented', i.e. be able to remain on their current treatment(s). However, if patients were to meet the proposed access criteria to new treatments (natalizumab, fingolimod) they could then switch to one of the newer agents. Members considered that once a patient moved to new funded treatments, under the suggested new criteria for accessing treatment with natalizumab or fingolimod, they should not be eligible to move back to as accessed under current existing Special Authority criteria.

- 2.18. The Committee considered paragraph 2.18 of the Neurological Subcommittee minutes. The Committee considered that the use of natalizumab and fingolimod later in the course of disease (EDSS >3.0) is likely to be less beneficial than if used earlier, and considered the proposed disability progression criterion of the entry criteria of EDSS 0 – 4.0 to be practical. The Committee considered that there would be an additional cost to the health sector to continue to treat after EDSS 4.0 with uncertain health gains, and that treatment should not be funded for patients with an EDSS score >4.0. The Committee noted that it could revisit the proposed entry criteria should new clinical evidence become available for RRMS that supports treatment later in the course of disease.
- 2.19. The Committee considered that there is no evidence at this time to support the use of the newer agents or the current agents once disease progression has occurred, and considered that appropriate stopping criteria should apply. The Committee noted that, in the pivotal trials of the new agents, progression of EDSS by 1.5 points has been used as an endpoint for disability progression. The Committee considered that, in practice, measuring disability progression may be too subjective for less severe EDSS progression and that the following steps should be used to define EDSS progression for a stopping criterion: 0 to 3.0, 1.0 to 3.0, 1.5 to 3.5, 2.0 to 4.0, 2.5 to 4.5, 3.0 to 4.5, 3.5 to 4.5, or 4.0 to 4.5.
- 2.20. The Committee considered that it would be appropriate for access to MS treatments (i.e. assessing whether patients meet entry and exit criteria) to continue to be managed by the Multiple Sclerosis Treatment Advisory Committee (MSTAC), due to the complexity and the potential for uncertainty in assigning scores in relation to MS disease metrics.
- 2.21. The Committee considered that the potentially large budget impact associated with funding either natalizumab or fingolimod, or both, and the relatively poor cost-effectiveness of the agents at the proposed prices may make it difficult for PHARMAC to progress funding. The Committee noted the potential for additional expenditure associated with the monitoring and administration costs for natalizumab and fingolimod, and the cost for treating progressive multifocal leukoencephalopathy (PML) should this occur with natalizumab. However, the Committee considered that these new criteria may enable the selection of patients who would benefit most from new treatments.
- 2.22. Members noted that updated analysis from the United Kingdom Risk Sharing Scheme is scheduled to be published this year and the funding of beta interferon or glatiramer acetate may need to be reviewed pending the outcome of that longitudinal follow-up of disease progression with MS treatments compared with historical controls. The Committee noted that the plan for the updated analysis from the United Kingdom Risk Sharing Scheme included a different set of historical control data than was used in the first report. The Committee considered the population included in the Risk Sharing Scheme to be similar to the MS population in New Zealand, and therefore the results from this study would be relevant to the New Zealand setting.
- 2.23. The Committee considered and agreed with the paragraph 2.27 of the Neurological Subcommittee minutes, that there is no robust evidence from randomised controlled trials to support the use of fingolimod or natalizumab in patients with clinically isolated syndrome but that evidence may emerge in the future. The Committee noted that treating patients after a single demyelination episode (in a clinically isolated syndrome), but before a diagnosis of definitive MS had been made, would risk unnecessarily treating some patients who do not progress to/go on to develop definite MS.

Other matters

- 2.24. Regarding items 5 and 6 (apixaban and rivaroxaban for stroke prevention in atrial fibrillation), the Committee deferred making any recommendations. The Committee requested that the funding applications for both products be reviewed at its May 2014 meeting.
- 2.25. The Committee noted and accepted item 7 (everolimus for the treatment of subependymal giant cell astrocytomas not amenable to neurosurgical resection) with the exception of recommendation 7.3. The Committee reviewed correspondence from the applicant requesting that the Special Authority include Paediatric Oncologists. The

Committee considered this to be an appropriate request as Paediatric Oncologists are likely to be involved with the treatment of these patients. The Committee **recommended** that Paediatric Oncologists be included as applicants in the proposed Special Authority Criteria.

Analgesic Subcommittee – 24 September 2013

- 2.26. The Committee noted and accepted items 1-9 with the exception of the recommendations in regards to tramadol oral drops (item 5.24).
- 2.27. Regarding item 5.24 of the Subcommittee minutes, the Committee expressed concerns around the availability of tramadol oral drops in the community, especially for use in the community-dwelling elderly population. The Committee considered that tramadol oral drops may be beneficial to the paediatric population in the community and that a restriction would need to be in place to ensure access was limited to this population. The Committee would need to consider the issue again if access needs to be widened to include adults.

Rheumatology Subcommittee – 4 October 2013

- 2.28. Regarding item 6.17 the Committee noted that the Subcommittee had recommended that New Zealand Rheumatology Association (NZRA) be approached to develop, and make available on its website, prescriber and patient information sheets for benzbromarone. The Committee noted that the NZRA had now included benzbromarone prescriber information and patient information on its website. Members noted that while the information on the NZRA website was helpful, the Committee could contact the NZRA to offer information which could strengthen the quality of the information available to prescribers and patients.
- 2.29. The Committee noted and accepted item 7 in relation to tocilizumab for the treatment of Rheumatoid Arthritis with the exception of the medium priority recommendation in 7.14. The Committee **recommended** that access to tocilizumab on the HML be widened with low priority.
- 2.30. The Committee noted and accepted the remainder of the record of the meeting.

Cancer Treatment Subcommittee – 13 September 2013

- 2.31. The Committee noted and accepted item 6 in relation to abiraterone for the treatment of metastatic castrate resistant prostate cancer (mCRPC). The Committee agreed with the Subcommittees recommendation that abiraterone should be funded for taxane naïve patients with low priority. However, in relation to item 6.11 the Committee considered that it was appropriate to fund abiraterone for the small group of taxane pre-treated patients as well, noting that the numbers of patients in this this small group would diminish over time if abiraterone were funded in the taxane naïve population. The Committee **recommended** that abiraterone should be funded subject to Special Authority criteria for taxane naïve and taxane-pretreated patients with low priority.
- 2.32. In relation to item 9.12, lenalidomide for multiple myeloma, the Committee **recommended** that PHARMAC seek advice from a specific named clinician regarding appropriate Special Authority wording to ensure that lenalidomide was targeted only to patients whose peripheral neuropathy contraindicated further treatment with thalidomide and/or bortezomib.
- 2.33. The Committee noted and accepted item 10 in relation to plerixafor for stem cell mobilisation with the exception of the recommendation in 10.17. The Committee **recommended** that the application be deferred pending MedSafe approval of plerixafor. The Committee would like to consider the application in full following MedSafe approval of plerixafor.
- 2.34. The Committee noted and accepted the remainder of the record of the meeting.

3. Correspondence

- 3.1. In addition to the correspondence regarding benzbromarone (4.1-4.3), the Committee discussed three further items of correspondence received, regarding melatonin, olmesartan and nab-paclitaxel.

6.2 Melatonin

- 3.2. The Committee noted that at its November 2012 review of melatonin for secondary insomnia in children and adolescents with neurodevelopmental or psychiatric comorbidities it had recommended that advice be sought from the Paediatric Society and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) regarding what the appropriate age cut-off for treatment should be and the appropriate treatment comparator.
- 3.3. The Committee noted the responses received from the Paediatric Society and the RANZCP in relation to melatonin.
- 3.4. The Committee accepted the advice from the Paediatric Society that behavioural and environmental approaches should be trialled, if appropriate, prior to initiation of treatment with melatonin.
- 3.5. The Committee **recommended** that melatonin be funded with a low priority, for secondary insomnia in children and adolescents with neurodevelopmental or psychiatric comorbidities subject to the following Special Authority criteria:

Initial application only from a psychiatrist or paediatrician or medical practitioner on the recommendation of a psychiatrist or paediatrician. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient has been diagnosed with persistent and distressing insomnia secondary to a Neurodevelopmental Disorder (such as Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder); and
2. Behavioural and environmental approaches have been tried or are inappropriate; and
3. Patient is aged ≤ 18 years.

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

1. Patient has been diagnosed with persistent and distressing insomnia secondary to a Neurodevelopmental Disorder (such as Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder); and
2. Behavioural and environmental approaches have been tried or are inappropriate; and
3. Patient is aged ≤ 18 years; and
4. Patient is continuing to benefit from treatment.

- 3.6. The decision criteria particularly relevant to this recommendation are : (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) the clinical benefits and risks of pharmaceuticals; and (vii) the direct cost to health service users.

6.3 Olmesartan

- 3.7. The Committee discussed an application for funding of olmesartan for sarcoidosis made by a representative on behalf of a group of patients.
- 3.8. The Committee noted olmesartan is not registered in New Zealand and is not listed on the Pharmaceutical Schedule. Members noted there are a number of other angiotensin II receptor antagonists registered and listed on the Pharmaceutical Schedule in NZ (candesartan, losartan). Losartan is listed in the schedule without restrictions. Members

noted that sarcoidosis is not an approved indication on the datasheets of angiotensin II receptor antagonists.

- 3.9. The Committee acknowledged the significant impact sarcoidosis has on patients and that there is an unmet clinical need for an effective treatment. The Committee noted the Marshall Protocol suggests angiotensin II receptor antagonists in general, and olmesartan in particular, may be immunomodulatory in patients with sarcoidosis. Members considered the quality and strength of evidence provided for angiotensin II antagonism and the Marshall Protocol in sarcoidosis to be weak.
- 3.10. The Committee considered there is insufficient evidence to support the funding of olmesartan for use in patients with sarcoidosis at this time.

Nab-paclitaxel

- 3.11. The Committee noted correspondence from [REDACTED], in response to its May 2012 minute regarding nab-paclitaxel. Members noted [REDACTED] had provided further information from the supplier regarding the use of nab-paclitaxel (Abraxane) in patients who had previously experienced hypersensitivity reactions (HSR) to paclitaxel or docetaxel.
- 3.12. The Committee noted that the evidence provided was limited to case reports and a retrospective chart review at a single centre of 110 patients with prior HSR to paclitaxel who were subsequently challenged with nab-paclitaxel. Members noted that some patients subsequently experienced HSR to nab-paclitaxel and that the supplier did not recommend, or condone, the use of nab-paclitaxel in any manner other than described in the product information, which includes a contraindication in patients who have had prior HSR to paclitaxel.
- 3.13. The Committee noted that PTAC's Cancer Treatments Subcommittee (CaTSoP) had reviewed the funding of nab-paclitaxel at the Subcommittee's September 2013 meeting. Members noted that the Subcommittee considered that 3 weekly paclitaxel was rarely used anymore, as weekly paclitaxel was more efficacious and less toxic and not associated with HSR, concluding that there was no advantage for nab-paclitaxel over weekly paclitaxel. The Committee noted and agreed with the Subcommittee's recommendation that nab-paclitaxel be funded only if cost neutral to weekly paclitaxel.

4. Pneumococcal vaccine for immunisation of over-65s

Application

- 4.1. The Committee considered an application from Merck Sharp and Dohme for the listing of pneumococcal vaccine polyvalent on the Pharmaceutical Schedule for the vaccination of all people in the 65 and over age group.

Recommendation

- 4.2. The Committee **recommended** that the application for pneumococcal vaccine polyvalent for people aged 65 and over be declined.
- 4.3. The Decision Criteria particularly relevant to this recommendation are: (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services,* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 4.4. The Committee noted that ESR reports indicate that the incidence of pneumococcal disease in New Zealand may be falling, with 240 cases being reported in 2009 reducing to 210 in 2012. The Committee noted the fall in reported cases is consistent with

international experience following the introduction of childhood pneumococcal conjugate vaccines. The Committee considered that with the 7-valent conjugated vaccine being introduced in New Zealand in 2008, and the 10-valent in July 2011, and the 13 valent vaccine in July 2014 (the reported cases of pneumococcal disease may continue to fall.

- 4.5. The Committee noted that the specific group applied for funding by the supplier has not been extensively studied, although the population studied by Ortqvist et al (Lancet. 1998;351(9100):399-403.) was close. Members noted that this prospective, multicentre, double-blind, randomised, placebo-controlled trial occurred in six tertiary-care or university hospitals in Sweden. 691 immunocompetent patients aged 50-85 years who had been treated as inpatients for community-acquired pneumonia (CAP) were randomly assigned either 23-valent pneumococcal capsular polysaccharide vaccine or placebo (sodium chloride). Members noted 57 (16%) of the 352 patients in the placebo group and) 63 (19%) of 339 patients in the vaccine group developed a new pneumonia, corresponding to a relative risk over time for the placebo group compared with the vaccine group of 0.83 (95% CI 0.58-1.12, p=0.31). Pneumococcal pneumonia was diagnosed in 16 (4.5%) patients in the placebo group and in 19 (5.6%) in the vaccine group, corresponding to a relative risk for the placebo group of 0.78 (95% CI 0.40-1.51, p=0.45). Members noted that there was no difference in the death rate between the two study groups.
- 4.6. The Committee noted a study by Maruyama et al. (BMJ 2010;340:c1004) This was a prospective, randomised, placebo controlled trial of 1006 nursing home residents randomly allocated to either 23-valent pneumococcal polysaccharide vaccine (n=502) or placebo (n=504). The primary end points were the incidence of all causes of pneumonia and pneumococcal pneumonia. Secondary end points were deaths from pneumococcal pneumonia; all causes of pneumonia, and non-pneumonia causes. Members noted that pneumonia occurred in 63 (12.5%) participants in the vaccine group and 104 (20.6%) in the placebo group. Pneumococcal pneumonia was diagnosed in 14 (2.8%) participants in the vaccine group and 37 (7.3%) in the placebo group (P<0.001). All cause pneumonia and pneumococcal pneumonia was significantly more frequent in the placebo group than in the vaccine group, with incidences per 1000 person years of 55 v. 91 (P<0.0006) and 12 v. 32 (P<0.001), respectively. Members noted that death from pneumococcal pneumonia was significantly higher in the placebo group than in the vaccine group (35.1% (13/37) v. 0% (0/14), P<0.01). The death rate from all cause pneumonia (vaccine group 20.6% (13/63) v. placebo group 25.0% (26/104), P=0.5) and from other causes (vaccine group 17.7% (89/502) v. placebo group (80/504) 15.9%, P=0.4) did not differ between the two study groups.
- 4.7. The Committee noted a population-based case-control study (Vila-Corcoles et al. BMC Infectious Diseases 2010, 10:73) that included 88 patients (cases) over 60 years of age with a laboratory confirmed invasive pneumococcal disease (IPD) (bacteraemic pneumonia, meningitis or sepsis) and 176 outpatient control subjects who were matched by primary care centre, age, sex and risk stratum. Members noted the pneumococcal vaccination rate was significantly lower in cases than in control subjects (38.6% vs 59.1%; p = 0.002). The adjusted vaccine effectiveness was 72% (OR: 0.28; 95% CI: 0.15-0.54) against all IPD and 77% (OR: 0.23; 95% CI: 0.08-0.60) against vaccine-type IPD. Vaccination was significantly effective against all IPD in both age groups: 60-79 years-old (OR 0.32; 95% CI: 0.14-0.74) and people 80 years or older (OR: 0.29; 95% CI: 0.09-0.91).
- 4.8. The Committee noted a matched case-control study in patients with community acquired pneumonia (CAP) admitted to five Spanish hospitals (Dominguez et al. Eur Respir J 2010;36:608-614). Cases were persons aged over 65 years admitted to hospital through the emergency department, who presented a clinical and radiological pattern compatible with pneumonia, were assessed using established criteria. Each case was matched with three control subjects by sex, age (± 5 years), date of hospitalisation (± 30 days) and underlying disease. The pneumococcal vaccination immunisation status of cases and controls was investigated. Members noted that 489 cases and 1467 controls were included in the final analysis. The Committee noted the overall adjusted vaccination effectiveness for all patients was 23.6% (95% CI 0.9-41.0) and that the adjusted vaccination effectiveness for immunosuppressed patients was 21.0% (95% CI -18.7-47.5).

- 4.9. The Committee noted a systematic review by Moberley et al (Cochrane Database Syst Rev, 2008 (1):CD000422) which assessed the effectiveness of pneumococcal polysaccharide vaccine in preventing pneumococcal-related morbidity and mortality in adults. Members noted that this was a meta-analysis of 15 randomised controlled trials (RCTs) (n = 48,656) and 7 non-RCTs (n = 62,294) to assess the effectiveness of pneumococcal polysaccharide vaccine in preventing pneumococcal-associated morbidity and mortality in adults. Meta-analysis of the RCTs indicated strong evidence of pneumococcal vaccine polyvalent efficacy preventing IPD with no statistical heterogeneity (OR 0.26, 95% CI 0.15 to 0.46; random-effects model, I-squared (I²) = 0%). Efficacy against all cause pneumonia was inconclusive with substantial statistical heterogeneity (OR 0.71, 95% CI 0.52 to 0.97; random-effects model, I² = 87.3%). Members noted that pneumococcal polyvalent vaccine was not associated with substantial reductions in all-cause mortality (OR 0.87, 95% CI 0.69 to 1.10; random-effects model, I² = 75.3%). The Committee noted that vaccine efficacy against primary outcomes appeared poorer in adults with chronic illness but the difference was not statistically significant. Non-RCTs provided evidence for protection against IPD in populations for whom the vaccine is currently utilised (OR 0.48, 95% CI 0.37 to 0.61; random-effects model, I² = 31.4%). The Committee considered the meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. Members considered that the evidence from RCTs is less clear with respect to adults with chronic illness. Members also considered that the meta-analysis does not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality
- 4.10. The Committee noted a meta-analysis of four studies of adults in high income countries with chronic illness in the Cochrane review, which involved 3000 patients, indicated no impact on IPD (OR 1.56 (0.35-6.94), all cause pneumonia (OR 0.97 (0.65-1.46)) and all-cause mortality (OR 1.04 (0.66-1.64)).
- 4.11. The Committee noted an online comment in the Cochrane review that the assessment of effectiveness of PPV is confined mainly to the results of a single study published six decades ago (Kaufman et al. Arch. IntMed. 1947;79:518-531). Members noted that this old study had no random assignment, no blinding of assessment, no placebo controls, and used only a three-serotype vaccine.
- 4.12. The Committee noted a paper by Elston et al (Epidemiol Infect. 2012;140(7):1252-66) which reported Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake in a region of the United Kingdom (UK) in the period 2002-2009. The Committee noted that although PPV23 uptake increased from 49% to 70% and paediatric PCV7 uptake reached 98% by 2009, the overall incidence of IPD increased from 11.8 per 100 000 to 16.4/100 000 (P=0.13), and the incidence of hospitalisation with pneumonia increased from 143/100 000 to 207/100 000 (P<0.001). Members noted that although a reduction in the proportion of IPD caused by PCV7 serotypes was observed, concurrent increases in PPV23 and non-vaccine serotype IPD contributed to an increased IPD burden overall. Marked inequalities in the geographical distribution of disease were observed.
- 4.13. The Committee noted the experience of PPV23 in the UK, where there was a phased introduction of the vaccine to those over the age of 80 in 2003, then those greater than 75 years in 2004 and finally to all those over 65 in 2005. The Committee noted that in March 2011 the Joint Committee on Vaccination and Immunisation (JCVI) subsequently concluded that there was a lack of impact, effectiveness and lack of long-lasting protection conferred by PPV 23 in the target population and also that there may be possibly an impaired response to re vaccination. The Committee noted a paper by Trotter et al (J Infect. 2010 ;60(3):200-8) which was used as a baseline for evaluating the impact of PPV23. The Committee noted that the JCVI concluded that there was little benefit from continuing the programme and advised that it be discontinued.
- 4.14. The Committee noted that, following a decision to discontinue the PPV23 programme in the UK, in line with the JCVI 2011 recommendation, submissions were made to the Pneumococcal Subcommittee of the JCVI and included an updated analysis that indicated an overall vaccine effectiveness of 24% but which considered that the vaccine may have been 48% effective in the first two years then reducing to 15% by year five. The Committee noted that, although the JCVI Pneumococcal subcommittee could not reach a

consensus on advice, in July 2011 the JCVI itself recommended that the existing routine universal programme for those aged 65 years and older should continue. The Committee considered that minutes from the JCVI (June 2012) reflect continued ambivalence and uncertainty related to the effectiveness of PPV23.

- 4.15. The Committee considered that the evidence for effectiveness of PPV23 at a population level was poor and the evidence for PPV23 in the elderly population was also poor.
- 4.16. The Committee considered that PPV23 would be given in conjunction with the influenza vaccine which may increase the uptake to ~ 70% over the next 5-10 years. The Committee noted that while the elderly and those with chronic disease are at the greatest risk of pneumococcal disease, these are also the groups with the least evidence for efficacy. [REDACTED]
- 4.17. The Committee noted that PHARMAC staff were unable to assess the CUA provided by Merck Sharp and Dohme or verify its results; the documentation provided gave insufficient information to understand the model's underlying structure and epidemiological assumptions, much of the model was hidden and could not be viewed, and that PHARMAC staff reported the applicant had not been able to address concerns raised by PHARMAC staff. The Committee considered in the future all applications with CUAs that are not accessible and/or documented should be referred back to the supplier as, particularly with vaccines, it is important that PHARMAC staff have the opportunity to reasonably access and assess accompanying CUAs to verify assumptions and validate mathematical models.

5. Aprepitant (Emend) for post-operative nausea and vomiting

Application

- 5.1. The Committee reviewed an application from a clinician for the funding of aprepitant for the prevention of postoperative nausea and vomiting (PONV)

Recommendation

- 5.2. The Committee **recommended** that aprepitant for the prevention of postoperative nausea and vomiting be funded within hospitals (Part II of Section H) with a low priority, subject to the following restrictions:

Indication – postoperative nausea and vomiting (PONV)

Prescriber: Anaesthetists

Dosage: Limited to one 40mg dose

Criteria: Any of the following:

1. Patient has a history of PONV refractory to at least two other antiemetic treatments; or
2. Both:
 - ii. Patient at high risk of PONV; and
 - iii. Scopolamine, droperidol or cyclizine are contraindicated; or
3. Patient at high risk of QT prolongation

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

- 5.4. The Committee noted that aprepitant is a substance P neurokinin 1 receptor antagonist and is currently listed in Section B and Part II of Section H for patients undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy for the treatment of malignancy.
- 5.5. The Committee noted that aprepitant is indicated for the prevention of PONV at a recommended dose of 40mg prior to anaesthesia.
- 5.6. The Committee considered three randomised controlled trials provided in the application.
- 5.7. Diemunsch et al. (Br J Anaesth. 2007;99:2:202-11) compared aprepitant 40 mg or 125 mg with ondansetron 4 mg IV. Aprepitant was reported to be significantly more effective than ondansetron for preventing vomiting at 24 hours and 48 hours after surgery, and in reducing nausea severity in the first 48 hours, but was non-inferior to ondansetron in achieving complete response 24 hours after surgery. Aprepitant was reported to be generally well tolerated.
- 5.8. Gan et al. (Anesth Analg. 2007;104:108-92) compared aprepitant 40 mg or 125 mg with ondansetron 4 mg IV. Aprepitant 40 mg was reported to be superior to ondansetron for prevention of vomiting in the first 24 hours and 48 hours but there were no significant differences in nausea control, use of rescue medication or complete response. No statistically significant side effect differences were reported.
- 5.9. Habib et al. (Anesth Analg. 2011;112:813-8) compared aprepitant 40 mg orally with ondansetron 4 mg IV. All patients received dexamethasone 10 mg after induction of anaesthesia. Aprepitant was reported to be superior to ondansetron for prevention of vomiting, but there were no significant differences in nausea control, use of rescue medication or complete response.
- 5.10. The Committee considered that the results of the above three trials suggested that the use of aprepitant for patients with a high risk of PONV resulted in approximately a 15% reduction in the incidence of vomiting. No statistically significant differences were seen for nausea control; use of rescue medication; or complete response. The Committee further examined indicative pooled results of the three RCTs. The Committee noted a modest relative risk for achieving complete response with aprepitant versus ondansetron of 1.07 (95% CI 0.88 – 1.30) (random effects model). The Committee noted that although the results were not statistically significant the confidence intervals appeared wide and were based on the submitted studies rather than a systematic review of all studies of this comparison.
- 5.11. The Committee considered the quality of the evidence to be good, with well-controlled randomised controlled trials. The trials had reasonable patient numbers examining relevant clinical outcomes including: vomiting, nausea control, use of rescue medication and complete response.
- 5.12. The Committee noted that the trials were conducted in populations at high risk of PONV, but this was not the same population in the application. The Committee also considered the application provided no evidence to support the assumed benefits of reduced PONV such as reduced anaesthesia costs, and reduced length of hospital stay. Members therefore considered the strength of the relevant evidence available to be moderate.
- 5.13. The Committee noted the comparator used in the trials, ondansetron 4mg IV, and considered that in everyday practice this dose would likely be higher. The Committee considered that the comparator treatments are likely to be ondansetron, cyclizine, droperidol and scopolamine patches used alone or in various combinations.
- 5.14. The Committee considered that there was no particular problem with access to currently funded treatments.

- 5.15. The Committee noted the high price of aprepitant compared with ondansetron. Members considered that if aprepitant 40mg was available it would most likely be used in combination with ondansetron and the other funded antiemetics and that this had high financial risk as there is questionable advantages of reduced vomiting. One Member considered the implication of poorly controlled vomiting may result in prolonged hospitalisation which may add to DHB costs.
- 5.16. The Committee considered that should aprepitant be funded for the prevention of PONV, patients would have this dispensed in the hospital. Members noted recent publications had investigated aprepitant 80 mg for the prevention of PONV, and the Committee considered that should aprepitant 40mg be funded, restrictions would need to be in place to ensure that increasing doses of aprepitant above 40mg did not occur
- 5.17. The Committee considered that PONV can be associated with an increased length of hospital stay and in theory if aprepitant reduced vomiting then shorter lengths of hospital stay may be possible although there was no empirical evidence to support or quantify this.
- 5.18. The Committee considered the population that would benefit most would be those with a history of PONV refractory to at least two other antiemetic treatments or those who are unable to take cyclizine, droperidol or scopolamine because of clinical risk factors.
- 5.19. The Committee noted there was no evidence included in the application to suggest a decreased risk of QT interval prolongation for those treated with aprepitant versus ondansetron. The Committee considered that if the use of aprepitant included an inclusion criterion for patients at risk of QT interval prolongation that this would be a large population exceeding 4000 patients per year.

6. Pertuzumab

Application

- 6.1. The Committee reviewed an application from Roche Products (New Zealand) Ltd for funding of pertuzumab (Perjeta) for the first-line treatment of patients with HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel. The Committee also reviewed a letter from the New Zealand Breast Cancer Special Interest Group in support of the application.

Recommendation

- 6.2. The Committee **recommended** that pertuzumab should be funded, when used in combination with trastuzumab for the first line treatment of patients with HER2-positive metastatic breast cancer. Members gave this recommendation a low priority.
- 6.3. The Committee **recommended** that pertuzumab should be funded subject to Special Authority criteria based on the patient population enrolled in the CLEOPATRA study, in particular that patients must be trastuzumab treatment naïve or have had an interval of at least 12 months between completion of the adjuvant trastuzumab therapy for early disease and diagnosis of metastatic breast cancer. The Committee further **recommended** that PHARMAC seek advice from the Cancer Treatments Subcommittee regarding the funding of pertuzumab compared with alternative treatment options, for example lapatinib in combination with trastuzumab and the above proposed special authority criteria.
- 6.4. The Decision Criteria particularly relevant to this recommendation are: *i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific Peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services; and (vi) the budgetary impact of any changes to the pharmaceutical schedule.*

Discussion

- 6.5. The Committee noted that HER2 positive breast tumours have a worse prognosis than HER2 negative tumours, as they are associated with poorly differentiated, high-grade tumours, high rates of cell proliferation and lymph-node involvement, and are relative resistance to certain types of chemotherapy. The Committee noted that Māori and Pacifica women have a higher prevalence of breast cancer in general, and of HER 2 positive breast cancers, compared with NZ European women. The Committee noted that currently funded first-line treatment options for patients with HER2-positive metastatic breast cancer comprise trastuzumab (Herceptin) or lapatinib (Tykerb).
- 6.6. The Committee noted that the key evidence provided in support of the application comprised a randomized, double-blind, placebo controlled, phase III study comparing trastuzumab plus docetaxel with pertuzumab plus trastuzumab, CLEOPATRA (Baselga et al. NEJM. 2012;336:109-19; Swain et al. Lancet Oncology 2013;14:461). Members noted that this study enrolled 808 patients with HER2-positive locally recurrent, unresectable or metastatic breast cancer who had not received prior chemotherapy or biologic therapy for their metastatic disease.
- 6.7. The Committee noted that patients may have received one hormonal treatment for their metastatic disease and may have received adjuvant, or neoadjuvant, chemotherapy with or without trastuzumab prior to randomization, with an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer. Members noted that approximately half of the patients enrolled had received prior neoadjuvant or adjuvant treatment, however, members noted that only 11% of patients received prior trastuzumab treatment. Members considered that this was not reflective of the current NZ population where the majority of patients would likely have received adjuvant trastuzumab treatment. Members noted other inclusion criteria included a left ventricular ejection fraction (LVEF) of 50% or more at baseline. The Committee noted exclusion criteria included central nervous system metastases or a previous decline in the left ventricular ejection fraction to less than 50% during or after prior trastuzumab therapy.
- 6.8. The Committee noted the primary end point of the study was progression-free survival, as determined on the basis of the assessment of tumours at an independent review facility. Secondary end points included overall survival, progression-free survival as assessed by the investigator, objective response rate, time to symptom progression, quality of life, cardiac outcomes and safety. Overall the Committee considered the strength and quality of the evidence for this study to be good.
- 6.9. The Committee noted that 406 patients were randomly assigned to placebo plus trastuzumab plus docetaxel (control group), and 402 to pertuzumab plus trastuzumab plus docetaxel (pertuzumab group). Members noted that patients received a loading dose of 8 mg of trastuzumab IV per kilogram of body weight, followed by a maintenance dose of 6 mg per kg every 3 weeks until disease progression, docetaxel was administered IV every 3 weeks at a starting dose of 75 mg/m² and pertuzumab or placebo was given at a fixed loading dose of 840 mg, followed by 420 mg every 3 weeks until disease progression or the development of toxic effects that could not be effectively managed. The Committee noted that treatment with pertuzumab improved prolonged progression-free survival by 6.1 months, from 12.4 months in the control group to 18.5 months in the pertuzumab group (hazard ratio for progression or death, 0.62 (95% confidence interval [CI], 0.51 to 0.75; P<0.001). Members further noted that after a median follow-up of 30 months overall survival favoured pertuzumab treatment with a hazard ratio of 0.66 (95% confidence interval [CI], 0.52 to 0.84; P<0.001). Members noted that at this timepoint 154/406 (38%) of control group had died compared to 113/402 (28%) of patients treated with pertuzumab, an absolute risk difference of 9.8% and a number needed to treat of 10.2. Median OS survival had not been reached in the pertuzumab arm and was 37.6 months in the control arm.
- 6.10. The Committee noted that patients in the control group received a median of 15 cycles of treatment compared with 24 cycles in the pertuzumab group. Members noted that there was no evidence of a worsening of cardiac function with pertuzumab, however, members

noted higher rates of diarrhoea in the pertuzumab group compared with the control group (all grades 67% vs. 46%).

- 6.11. The Committee noted that quality of life (QoL) evidence from the CLEOPATRA study (Cortes et al. Ann Oncology. 2013;24:2630-5) indicated that pertuzumab did not have a detrimental effect on patients' quality of life. However, members considered that the evidence was of poor quality and there was a significant chance of bias for this data as there was only 75% completion rate and it was limited to patients who did not experience disease progression.
- 6.12. The Committee noted other studies examining QoL outcomes in breast cancer patients including Lloyd et al. (Br J Cancer; 2006;95:683-90) which estimated a treatment utility of 0.72, with a gain of 0.07 for treatment response and a decline of 0.27 for disease progression. Members noted that the study identified declines in utility due to treatment related toxicities of between 0.10 (diarrhoea/vomiting) and 0.15 (febrile neutropenia).
- 6.13. The Committee considered it would be appropriate for PHARMAC's cost utility analysis to include QoL decrements for adverse events relating to pertuzumab treatment. In particular the Committee considered a QoL decrement of 0.10 relating to pertuzumab-related diarrhoea would be appropriate. However, the Committee did not consider that it was possible to estimate confidence intervals around this estimate from the evidence considered.
- 6.14. The Committee considered that overall the evidence demonstrated that pertuzumab improved progression free survival and overall survival, however, members considered that it was likely that the benefits in the New Zealand population may not be as high as seen in the CLEOPATRA study given the higher proportion of patients in New Zealand that would have received prior adjuvant trastuzumab treatment compared with the study population. Members noted that pertuzumab treatment was very expensive and it was not curative, members further noted that treatment with pertuzimab would also increase treatment duration, and therefore cost, of currently funded trastuzumab.
- 6.15. The Committee considered that the treatment of metastatic breast cancer was rapidly evolving and there was evidence supporting survival gains with other treatments in this setting.

7. Bevacizumab for the first-line treatment of advanced/metastatic ovarian cancer

Application

- 7.1. The Committee reviewed an application from Roche Products (New Zealand) Ltd for the funding of bevacizumab (Avastin), in combination with carboplatin and paclitaxel, for the first-line treatment of untreated advanced (FIGO Stage IIIB or IIIC, sub-optimally debulked (maximum diameter of any gross residual disease > 1cm)), or metastatic (FIGO stage IV), epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recommendation

- 7.2. The Committee **recommended** that the application for the funding of bevacizumab for patients with treatment naïve advanced or metastatic epithelial ovarian, fallopian tube or primary peritoneal cancer be declined.
- 7.3. The Committee **recommended** that the funding of bevacizumab for this indication should be reviewed by Cancer Treatments Subcommittee of PTAC (CaTSoP) when final data from the ICON7 study have been published.
- 7.4. The decision criteria particularly relevant to this recommendation are : *(i) the health needs of all eligible people within New Zealand; (ii) the particular health needs of Māori & 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

- 7.5. The Committee noted that bevacizumab is currently listed on the Hospital Medicines List for the treatment of patients with ocular neovascularisation or exudative ocular angiopathy, both of which were off label uses.
- 7.6. The Committee noted that the application requested funding for a dose that was lower and for a shorter duration compared with the Medsafe approved Datasheet dosing recommendation for patients with ovarian cancer. Members considered this had the advantage of lower costs but that the need to assess evidence for efficacy at this lower dose.
- 7.7. The Committee noted that key evidence provided in support of the funding being requested comprised an exploratory planned subgroup analysis from a randomised, open label, phase III study comparing combination chemotherapy comprising carboplatin and paclitaxel with, and without, bevacizumab, the ICON7 study (Perren et al. NEJM. 2011;365:2484-2496; unpublished final analysis in the form of slides presented at European Cancer Congress (ECC) 2013). Members noted that this study enrolled 1528 patients with histologically confirmed, high risk, early-stage disease (FIGO stage I or IIA and clear- cell or grade 3 tumours) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer who had undergone debulking surgery. Members noted that patients were randomised in a 1:1 ratio to receive carboplatin (AUC 5 or 6) plus paclitaxel (175mg/m²) (CP) (n=764) every three weeks for 6 cycles or the same regimen plus bevacizumab (CPB) (n=764). Bevacizumab was administered at 7.5 mg/kg, given concurrently with chemotherapy every 3 weeks for 5 or 6 cycles and then continued as monotherapy for up to a further 12 additional cycles or until disease progression whichever occurred earlier. Members noted that more than 90% of the women in both groups completed the first 6 cycles of bevacizumab in combination with carboplatin and paclitaxel and 62% received bevacizumab through to cycle 18. Members noted that median duration of bevacizumab treatment was 16-17 cycles.
- 7.8. The Committee noted that the primary endpoint of the study was progression-free survival (PFS) based on investigator assessment, with overall survival (OS), quality of life and safety analyses also performed. Members noted that in the primary analysis, performed after median follow-up of 19 months, the addition of bevacizumab improved median PFS by 1.7 months (PFS 19 months CPB vs. 17.3 months Hazard Ratio 0.81; 95% CI, 0.70 to 0.94; P = 0.004) but median Overall Survival (OS) had not been reached at this time point in either arm. The Committee considered that the evidence suggested that bevacizumab treatment effect appeared to maximise at 12 months, coinciding with the end of treatment.
- 7.9. Members noted that a pre-planned analysis of PFS for 502 patients with high risk disease was also undertaken (high risk defined as FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery as per the proposed funding). Members noted that in this high-risk subgroup analysis bevacizumab improved median PFS by 5.5 months (16 months CPB vs 10.5 months CP HR 0.73; 95% CI, 0.60 to 0.93; P = 0.002) and improved median OS by 7.8 months (36.6 months CPB vs 28.8 months CP HR 0.64; 95% CI, 0.48 to 0.85; P = 0.002).
- 7.10. The Committee noted that an unpublished final analysis, performed after median follow-up of 49 months, demonstrated a 2.4 month improvement in PFS in the all patient population (19.9 months CPB vs 17.5 months CP) but no difference in median overall survival between the treatment groups. Members noted that in the high risk subgroup group analysis at this time point median PFS was increased 5.5 months (16 months CPB vs. 10.5 months CPB, HR=0.73, 95% CI 0.61-0.88; P=0.001), median OS was 30.3 months in the CP arm and 39.7 months in CPB arm (HR=0.78, 95% CI 0.63-0.97; P=0.03).
- 7.11. The Committee noted that bevacizumab treatment was associated with a small but clinically significant decrement in Quality of Life (QOL) compared with standard treatment. Members considered that increased adverse events and the need for continued hospital

treatment likely contributed to the lower QOL seen in bevacizumab treated patients. The Committee was disappointed that QOL assessments were stopped at disease progression and not continued throughout the study.

- 7.12. The Committee considered supportive evidence from the pivotal registration study for bevacizumab in ovarian cancer, GOG-0218 (Burger et al. NEJM. 2011;365:2473-83). However, members noted that this study used dosing of 15mg/kg bevacizumab as opposed to 7.5 mg/kg proposed in the supplier's application. Members noted that this was a phase III, double blind, randomised, placebo-controlled, multicentre, 3-arm trial of first-line bevacizumab in 1,873 patients with previously untreated stage III (incompletely resectable) or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer. All patients received standard chemotherapy comprising carboplatin (AUC 6) plus paclitaxel (175 mg/m²) every 3 weeks for 6 cycles plus a study treatment for cycles 2 through 22, with each cycle of 3 weeks duration for total treatment duration of 15 months. The control treatment arm was chemotherapy with placebo added in cycles 2 through 22 (CP arm, n=625), the bevacizumab-initiation treatment arm was chemotherapy with bevacizumab (15 mg/kg) added in cycles 2 through 6 and placebo added in cycles 7 through 22 (CPB initiation arm n=623) and the bevacizumab-throughout treatment arm was chemotherapy with bevacizumab (15 mg/kg) added in cycles 2 through 22 (CPB15 throughout arm n=623). Members noted that two thirds of the patients enrolled in GOG-0218 had 'high risk' disease characteristics consistent with the funding application.
- 7.13. The Committee noted that the primary endpoint of the study was initially Overall Survival, but this was replaced during the study by progression free survival. Members noted that following disease progression blinding was lifted and patient's treatment could be modified. Members noted that median PFS was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group, and 14.1 in the bevacizumab-throughout group. As compared with the control group, the hazard of progression or death was not significantly different in the bevacizumab-initiation group (HR 0.908; 95% confidence interval [CI], 0.795 to 1.040; P = 0.16) but significantly lower in the bevacizumab-throughout group (HR 0.717; 95% CI 0.625 to 0.824 p<0.001). Members noted maximal separation of the PFS curves occurred at 15 months, coinciding with the end of treatment and converging 9 months later. Members noted no difference between treatment groups for median Overall Survival and considered data confounded by multiple treatments being used following disease progression. Members noted that quality of life improvement during the chemotherapy phase was slightly lower in the bevacizumab treated patients versus the control but the considered that clinical significance of this result was unclear.
- 7.14. The Committee noted that bevacizumab treatment was associated with a number of serious adverse effects including bleeding, hypertension, gastrointestinal perforations, thrombotic events, wound healing complications and neutropenia.
- 7.15. Overall, the Committee considered that the strength of evidence provided in support of the application was moderate and of low quality, comprising multiple analyses of sub-populations over various time points with various dosing regimens. Members considered that whilst there was limited evidence that bevacizumab improved progression free survival in high risk patients it was associated with a decline in overall quality of life and serious adverse effects. Members noted that bevacizumab was a high cost medicine and considered it unlikely to be cost-effective given the available evidence provided.

8. Ipilimumab for previously treated unresectable stage IIIc or IV melanoma

Application

- 8.1. The Committee considered a resubmission from Bristol-Myers Squibb (NZ) Limited for the listing of ipilimumab (Yervoy) on the Pharmaceutical Schedule for the treatment of patients with previously treated unresectable Stage IIIc or IV melanoma. The Committee also reviewed a letter provided in support of the application from a clinician.

Recommendation

- 8.2. The Committee **recommended** that the application be declined. The Committee further **recommended** that the application be referred to the Cancer Treatments Subcommittee for review once longer term data from the randomised study had been provided.
- 8.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; 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 noted that it had previously considered the funding of ipilimumab at its August 2012 meeting where it recommended that the application be declined and referred it to the Cancer Treatments Subcommittee. Members noted that CaTSoP considered the application at its October 2012 meeting where it also recommended that the application be declined.
- 8.5. The Committee noted that in its resubmission the supplier had provided additional evidence in response to concerns raised by PTAC and CaTSoP regarding the long term efficacy and autoimmune toxicity profile of ipilimumab. Members also noted that the supplier had also proposed a lower price for ipilimumab and a revised budget impact and cost-utility analysis.
- 8.6. The Committee reviewed long term overall survival evidence from a pooled analysis of patients enrolled in 12 ipilimumab studies with up to 10 years follow-up. Members considered that the evidence presented supported approximately 20% long term survival in patients treated with ipilimumab. Members noted that the supplier compared this long term ipilimumab survival data with a modelled predicted survival curve for patients receiving best supportive care.
- 8.7. The Committee considered it likely that ipilimumab was associated with some long term survival advantage over best supportive care but remained uncertain of the magnitude of benefit. Members considered that whilst the pooled analysis provided a large volume of data it was of poor quality because there was no control group. Members considered that longer term follow-up overall survival data from the pivotal randomised study previously published by Hodi et al. (N Eng J Med 2010;363(8):711-23) would provide much better quality of evidence of benefit of ipilimumab over best supportive care. Members questioned why the supplier had not provided this data and had in fact stated that further follow-up on this cohort would not be undertaken. Members considered that longer term overall survival data from the Hodi study should be provided for its consideration, and considered that it would be feasible for the supplier to do so.
- 8.8. The Committee noted further information provided by the supplier regarding the auto-immune toxicity profile of ipilimumab which included expert statements from various clinicians with experience of treating patients with ipilimumab. Members considered that whilst the proportion of patients who experienced adverse events was similar to other chemotherapy agents the specific, and new, profile of ipilimumab-associated adverse events meant that comprehensive clinician and patient education was critical. In particular, members considered that careful long term follow-up of patients treated with ipilimumab was important because of the potential for chronic, or late, auto-immune toxicities that have a different profile to the acute toxicities commonly seen with most chemotherapy agents that oncologists would be familiar with.

9. Febuxostat for treatment of gout

Application

- 9.1. The Committee considered a further application from TeArai BioFarma for the listing of febuxostat (Adenuric) on the Pharmaceutical Schedule for the treatment of hyperuricaemia in patients with gout. Members noted that the supplier was requesting a high priority recommendation for febuxostat in two populations: second-line after allopurinol, and first-line in patients where allopurinol has an unfavourable risk-benefit profile.

Recommendation

- 9.2. The Committee **recommended** that febuxostat be listed in the Pharmaceutical Schedule for the treatment of severe refractory gout, with a medium priority subject to the following Special Authority criteria.

Initial application from any relevant practitioner. Applications valid for 6 months for applications meeting the following criteria:

1. Patient has had 3 or more confirmed episodes of symptomatic gout; and
2. Either:
 - 2.1 The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses titrated to of at least 600 mg/day and appropriate doses of probenecid; or
 - 2.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and serum urate remains greater than 0.36 mmol/l despite appropriate doses of probenecid.

Renewal from any relevant practitioner. Applications valid for 2 years for applications where the treatment remains appropriate and the patient is benefitting from treatment.

- 9.3. The Committee **recommended** that the application for funding of febuxostat for first-line treatment where the use of allopurinol has an unfavourable risk-benefit profile be declined.
- 9.4. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori 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.*

Discussion

- 9.5. The Committee noted that there was limited new evidence provided in the application. The Committee reiterated its view that gout was a significant public health issue particularly among Pacific and Māori peoples, and that the goal of urate-lowering treatment was to prevent, or reduce the frequency of, acute gout attacks and reduce the size and/or number of clinically detectable urate crystal deposits (tophi).
- 9.6. The Committee considered that most studies of febuxostat used suboptimal doses of allopurinol (up to 300 mg/day) as the comparator, and that whilst febuxostat dosing did not require dose titration, which was an advantage over allopurinol, it was more expensive than allopurinol or probenecid. The Committee also had concerns over the safety of febuxostat regarding the elevation of liver enzymes in 3–5% of patients and a non-significant but higher rate of death and cardiovascular events compared with allopurinol 300 mg. Members noted the EMEA restriction on the use of febuxostat in patients with severe cardiovascular disease. Overall, members considered that the full safety profile of febuxostat had yet to be established.

- 9.7. The Committee noted that allopurinol was associated with rare but potentially fatal, severe cutaneous adverse reactions (SCAR). Members considered that HLA-B*5801 was a clear risk factor for SCARs with a positive predictive value of approximately 1.5%, and a negative predictive value of 100%, in Han-Chinese populations. However, members noted the evidence in European populations was less clear and therefore considered that HLA-B*5801 testing in the NZ population would not be cost-effective and would be of limited predictive value. Members further noted that in a case series of patients with allopurinol associated SCAR, 1 of 13 patients also had a serious reaction to subsequent febuxostat treatment. The Committee considered that allopurinol associated SCAR could be managed through careful dose titration or desensitisation protocols.
- 9.8. The Committee considered that taking into account efficacy, safety and cost, allopurinol remained the first-line treatment of choice for patients with gout. However, members considered that a significant number of patients on allopurinol were being under-treated and that further education of prescribers, pharmacists and other health workers was required. Members considered the most important issue to address in order to improve health outcomes in gout patients was appropriate dosing of allopurinol rather than the need for new treatment options. Members noted that whilst benzbromarone had previously been funded to address the apparent high unmet medical need for new treatment options for gout, its uptake had been very low; members considered that this low uptake may be due either to patient access barriers associated with this medicine being unregistered, and therefore subject to requirements under Section 29 of the Medicines Act, or to the unmet need for new treatments being not as high as had been estimated previously.
- 9.9. The Committee noted that its previously recommended Special Authority criteria for febuxostat inadvertently did not require a confirmed diagnosis of gout, which the Committee considered important as there may be other, non-gout, reasons for patients presenting with increased serum urate levels where treatment with febuxostat, or other anti-gout treatments, may not be appropriate.
- 9.10. The Committee considered that in patients with renal impairment, effective treatment to reduce serum urate levels was particularly important. Members noted a number of studies of allopurinol use in patients with chronic kidney disease (reviewed in Bellomo World J Nephrol 2013; 2(2) 17-25), which reported improvement in renal function and no significantly increased risk of adverse reactions. Members considered that there was evidence to support using allopurinol above the dose based on creatinine clearance in patients with renal impairment (e.g. Stamp et al. Arthritis Rheum 2011;63:412-21).
- 9.11. Members considered that although probenecid was contraindicated in patients with renal stones and in patients with urate nephropathy, it could be used in patients with moderate renal impairment. The Committee also noted that benzbromarone is apparently effective and safe in patients with mild-to-moderate renal impairment, but considered the literature to be of moderate quality at best (Nucleosides Nucleotides Nucleic Acids. 2011;30:1035-8; Ann Rheum Dis. 1998;57:545-9) ; J Clin Rheumatol. 1999;5:49-55; Drug Saf. 2008;31:643-65). The Committee noted that the 2007 British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout (Rheumatology (Oxford). 2007;46:1372-4) recommends using benzbromarone as first-line treatment in patients with renal impairment.
- 9.12. The Committee considered that there was reasonable evidence in support of the use of febuxostat in mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min); however, on balance, the Committee considered that there was insufficient justification to recommend its use in this setting with a high priority as requested by the supplier.
- 9.13. The Committee noted the supplier's view on the cost of febuxostat compared with other treatment options that took into account lower dosing (40 mg) in a proportion of patients. However, members noted that a 40 mg febuxostat tablet was not available and considered that most patients would likely take one 80 mg tablet daily, or split the tablet for a 40 mg dose and discard the other half tablet, in which case a lower average treatment cost for febuxostat would not be achieved in practice. The Committee considered that having a 40 mg tablet available would be appropriate.

- 9.14. The Committee considered it would not be necessary to further review its recommendations for the funding of febuxostat unless significant new data became available or PHARMAC staff request further specific advice.

10. Rituximab (Mabthera) for polyarticular juvenile idiopathic arthritis (JIA)

Application

- 10.1. The Committee considered an application from a clinician for the funding of rituximab (Mabthera) for the treatment of patients with polyarticular juvenile idiopathic arthritis (pJIA) unresponsive to adalimumab or etanercept, or in whom the use of TNF inhibitors is contraindicated.

Recommendation

- 10.2. The Committee **recommended** that the application be declined.
- 10.3. The Committee **recommended** that the applicant resubmits the application clarifying the population being requested for funding, the role of other oral DMARDs prior to initiation of biologics, and considering the appropriateness of tocilizumab funding for this population.
- 10.4. The Decision Criteria particularly relevant to this recommendation are: *i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific Peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services; and (vi) The budgetary impact of any changes to the Pharmaceutical Schedule.*

Discussion

- 10.5. The Committee noted that at its October 2013 meeting the Rheumatology Subcommittee of PTAC noted that rituximab was now available on the HML for use in rheumatoid arthritis where TNF inhibitors were contraindicated or had been ineffective and considered that it would be useful to also have access to rituximab as a second-line biologic option for patients with juvenile idiopathic arthritis (JIA). Members noted that the applicant considered that children were disadvantaged compared with adults with rheumatoid arthritis as they have no access to second-line biologic treatment with rituximab.
- 10.6. The Committee noted that there are seven subtypes of juvenile idiopathic arthritis (JIA): oligoarticular (the most common subtype), polyarticular (Rheumatoid Factor [RhF] negative), polyarticular (RhF positive), systemic (sJIA), enthesitis-related (previously known as juvenile spondyloarthritis), psoriatic and undifferentiated arthritis. Members considered that children diagnosed with polyarticular JIA (pJIA) may actually have the adult form of rheumatoid arthritis at an earlier-than-usual age.
- 10.7. The Committee noted that adalimumab and etanercept were currently funded for patients with JIA (all subtypes) and that tocilizumab was also funded for patients with systemic JIA, subject to certain Special Authority criteria. Members noted that whilst tocilizumab was indicated for pJIA PHARMAC had not received a funding application for this population and it was currently more expensive than rituximab.
- 10.8. The Committee noted that the evidence provided by the applicant in support of the application comprised a small uncontrolled study conducted in a single centre in Russia (Alexeeva et al Clin Rheumatol 2011;30:1163-1172) and three case studies. Members noted that the Alexeeva study investigated the effect of up to four courses of rituximab (375 mg/m² infusions given once per week for four weeks) given 24 weeks apart in 55 patients aged 2 to 17 years. The study enrolled patients who were refractory or intolerant to previous DMARD treatment (steroids, NSAIDs and at least 2 immunosuppressants including methotrexate) and TNF inhibitors (either adalimumab, etanercept or infliximab).

- 10.9. The Committee questioned the relevance of the study to the patient population being requested for funding. Members noted that the majority of patients enrolled in the study had systemic JIA (46 patients) with only a small proportion having polyarticular JIA (7 patients) with the remaining having oligoarticular JIA (2 patients). In addition members noted that whilst the study reported that 25 patients had received prior infliximab treatment it was not clear if the remaining 30 had received any prior TNF inhibitor exposure or not. Members further noted that one-third of the 25 patients who had prior infliximab appeared to have discontinued infliximab due to adverse effects rather than lack of efficacy.
- 10.10. The Committee noted that efficacy analyses were performed after 12, 24, and 48 weeks in 55 children and after 72 and 96 weeks in 25 children. Members noted that primary endpoint (30% improvement according to ACR criteria) was achieved in 98% of patients at week 24. Remission at some time-point was recorded in 98% of patients at 96 weeks, however, members noted that because only 25 patients were assessed at this time point the long term outcome in the remaining 30 patients was unclear.
- 10.11. The Committee noted that 9 patients withdrew due to lack of efficacy or treatment intolerance. Members noted that 31% of patients experienced neutropaenia, 20% had reduced immunoglobulin levels and there was a high incidence of infections.
- 10.12. The Committee considered that overall the study was of poor quality and of limited relevance to the patient population being requested for funding given the very low numbers of patients with pJIA being enrolled in the study (n=7).
- 10.13. The Committee noted that rituximab was not indicated for the treatment of paediatric patients and were concerned about the potential for rituximab to cause prolonged immunosuppression as a result of B-cell depletion in their developing immune systems. Members questioned why funding for tocilizumab rather than rituximab in this population had not been sought given that there was better data for tocilizumab and this product was approved for the treatment of children with pJIA.
- 10.14. The Committee considered comparative trials against other funded oral immunosuppressants, for example leflunomide, azathioprine, mycophenolate and sulphasalazine as discussed in Review of Disease-Modifying Anti Rheumatic Drugs in Paediatric Rheumatic disease (18th Expert Committee on the Selection and Use of Essential Medicines 2011) should be provided.
- 10.15. The Committee considered that individual applications for tocilizumab for pJIA could be assessed on a case by case basis via the NPPA process as it is an approved indication. If new evidence for rituximab for pJIA emerges the application for rituximab could also be considered through NPPA.

11. Nicotine inhaler (Nicorette Inhalator)

Application

- 11.1. The Committee considered an application from the West Coast Tobacco Free Coalition and Waikato DHB Smokefree Coordinators and smoking cessation practitioners for the funding of nicotine inhaler (Nicorette Inhalator) for community use.

Recommendation

- 11.2. The Committee **recommended** that the application for funding of nicotine inhaler (Nicorette Inhalator) for community use be declined.
- 11.3. The decision criteria particularly relevant to this recommendation are : *(i) the health needs of all eligible people within New Zealand; (ii) the particular health needs of Māori & Pacific peoples; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) the clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding*

pharmaceuticals rather than using other publicly funded health and disability support services; 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

- 11.4. The Committee noted that tobacco smoking is the leading cause of preventable deaths among New Zealanders and is a recognised risk factor for a wide range of diseases including numerous cancers, heart disease, respiratory disease, blindness and stroke. The Committee noted that smoking cessation is an important health target for New Zealand and is a Government health priority. The Committee noted that Māori adults still have the highest prevalence of daily smoking.
- 11.5. The Committee noted that the average ex-smoker will make around 14 quit attempts with pharmacological support and that nicotine replacement therapy (NRT) has an important part to play in supporting smokers to quit. The Committee considered that, in addition to the currently funded pharmacological treatments NRT (patches, gum and lozenges), nortriptyline, bupropion and varenicline, reducing the prevalence of cigarette smoking relies on price control, legislative and societal changes.
- 11.6. The Committee noted that nicotine inhalers consist of a plastic tube with a plug of nicotine and menthol at one end through which the user inhales, which replicates the hand-to-mouth action of smoking and provides upper airways stimulation. However, the Committee noted that inhalers produce gas-phase nicotine which deposits in the oral mucosa rather than the lung, which results in different pharmacokinetics and pharmacodynamics compared with smoking. The Committee raised concerns with the appearance of the inhaler, noting that it looked like a child's toy. The Committee considered that there may be risks associated with the appearance and this could encourage paediatric consumption of the product.
- 11.7. The Committee noted its previous discussion on the nicotine inhaler. The Committee noted that the previous recommendation to decline the funding application for nicotine inhaler in the community was made primarily on the basis that there was no strong evidence that inhaled preparations are more effective than the currently funded forms of NRT and that funding additional NRT preparations would be associated with considerable expenditure without significant additional health gain.
- 11.8. The Committee noted that the applications provided anecdotal evidence from inpatients and smoking cessation providers that smokers prefer nicotine inhalers to the lozenges and gum. The Committee considered that the evidence that had been supplied in relation to the acceptability of the nicotine inhaler was weak and of low quality. The Committee considered that patient acceptance is key to more smokers using NRT to support a quit attempt; however, the Committee considered that there is little high quality evidence in the scientific literature examining patient acceptance of different forms of NRT and how this translates to successful quit attempt rates.
- 11.9. The Committee noted a study by Fagerstrom et al. (Tobacco Control 1997;6:2033-8) in which five NRT formulations were tested during a two week crossover trial involving 170 subjects. The Committee noted that inhalers were rated to be the least helpful for smoking cessation.
- 11.10. The Committee noted a study by Schneider et al. (Am J Behav Sci. 2004;28(10):72-86) which tested preferences among five NRT formulations used *ad libitum* for half a day; the inhaler was preferred by 49% of the 48 participants. However, the investigators commented that they did not observe how the treatments were used so the inhalers may have been puffed less frequently than advised, which may have resulted in the fewer side-effects and reduced relief of withdrawal symptoms observed in these patients.
- 11.11. The Committee noted a follow up study by Schneider et al. (Psychopharmacology 2005;182:545-550) repeating the previous study, but this time with enforcement of proper use. The authors concluded that gum was preferred over inhaler for ease of use, safety and use in public and the inhaler ranked last on relief of withdrawal, use under stress and choice to help quit. The Committee noted another study of similar design by the same

authors (Schneider et al. Psychopharmacology 2006;187:476-485) in which the inhaler with patch was preferred for “use under stress” but was ranked last on “safest to use”. The Committee noted the authors comment that embarrassment with inhaler use was consistently expressed and linked to the general awkwardness with shallow puffing, inability to inhale deeply and its appearance.

- 11.12. The Committee noted a study by Hajek et al. (Arch Int Med. 1999;159:2033-8) in which 504 smokers who wanted to quit were randomised to receive either gum, patch, inhaler or nasal spray. The authors reported no difference between the products in their effects on withdrawal discomfort, perceived helpfulness or efficacy.
- 11.13. The Committee noted that the previously available nicotine inhaler contained 10 mg of nicotine and that this had been replaced by a 15 mg nicotine inhaler. The Committee considered that it could not be assumed that a higher strength inhaler would produce a greater effect. The Committee noted the information provided in the Medsafe data sheet that indicated that both the 10 mg and 15 mg inhaler typically produce nicotine plasma levels of 6-8 ng/ml and considered that this indicates that both the 10 mg and 15 mg inhalers produce a similar therapeutic effect.
- 11.14. The Committee considered that the PHARMAC staff estimation that patients using a nicotine inhaler for smoking cessation would use 3 x 15 mg cartridges per day was conservative. The Committee noted that during a double-blind placebo-controlled trial (Bolliger et al BMJ. 2000;321:329-333), 117 subjects used a mean of 4.3 x 10 mg inhaler cartridges per day (standard deviation (SD) 2.2) in the first 6 weeks. The Committee noted that during a further double-blind placebo-controlled trial (Rennard et al. Nicotine Tob Res 2006;8:555-64), 215 subjects used a mean 6.4 x 10 mg inhaler cartridges per day (SD 2.7, range 2-12). The Committee considered that, should nicotine inhalers be used as directed, between 4 and 6 cartridges at a dose of between 10 mg and 15 mg per day was a more accurate estimate.

12. TNF alpha inhibitors for seronegative spondyloarthropathies

Application

- 12.1. The Committee considered an application from a clinician for the funding of TNF-alpha inhibitors (adalimumab, etanercept or infliximab) to be widened to include seronegative spondyloarthropathies (SpAs), specifically undifferentiated spondyloarthritis (u-SpA) and inflammatory bowel disease associated arthritis (IBD-A).

Recommendation

- 12.2. The Committee **recommended** that the application for the funding of TNF alpha inhibitors for undifferentiated spondyloarthritis (u-SpA) be declined.
- 12.3. The Committee **recommended** that the application be referred to the Rheumatology Subcommittee for further advice regarding the disease state, the benefits of early TNF treatment in this setting, if there were ways to predict those patients likely to progress and specific Special Authority criteria.
- 12.4. 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; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services..
- 12.5. The Committee **recommended** that the funding of TNF alpha inhibitors (at least one of adalimumab or infliximab) should be widened to include inflammatory bowel disease-associated arthritis (IBD-A) with a low priority.

- 12.6. The Committee **recommended** seeking advice from the Rheumatology Subcommittee on appropriate Special Authority criteria.
- 12.7. The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; ((iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.

Discussion

- 12.8. The Committee noted that the spondyloarthropathies (SpAs) comprised a group of interrelated rheumatic conditions distinct from other types of inflammatory arthritis. Members noted there were five sub-classifications of SpA: ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease associate arthritis (IBD-A), post-infection reactive arthritis (ReA) and undifferentiated spondyloarthritis (u-SpA). The Committee discussed evidence and treatment options for uSpA and IBD-A separately:

u-SpA

- 12.9. The Committee noted that the pivotal registration trials for TNF-alpha inhibitors were conducted in AS and PsA patients for whom etanercept and adalimumab are funded through Special Authority. Members noted that approximately 25% of patients with SpA present with u-SpA and considered that whilst it was variable in severity and clinical outcome it was not fundamentally different from other SpA subtypes (i.e. AS or PsA). Members considered that a substantial proportion of patients their u-SpA will eventually evolve to definite AS or PsA .
- 12.10. The Committee noted that there was limited evidence for the use of TNF inhibitors in u-SPA mainly comprising small subgroups of patients enrolled in larger studies, small cohort studies and case reports. Overall members considered that whilst TNF treatment response in u-SpA appeared similar to PSA and AS the evidence supporting the effectiveness of TNFs in u-SpA was of low to moderate strength and quality.
- 12.11. The Committee considered that there was a need for better evidence to support the use of TNFs in patients with u-SpA to confirm the findings in smaller studies. Members noted that TNF inhibitors were associated with a risk of infections. Members considered there was a risk of slippage to other non-indicated forms of arthritis/spondyloarthropathies if the Special Authorities was widened to include u-SpA. Members were uncertain about the severity of pain and disability that patients with u-SpA experienced and questioned the value of early initiation of TNF treatment in these patients. Members questioned if there was evidence to support the view that early initiation of TNF treatment in u-SpA prevented future joint destruction and disability. Members were unsure if there was any way to predict which patients would likely to progress to AS or PsA from those with stable u-SpA, e.g using MRI imaging. The Committee considered further advice on these matters was needed from the Rheumatology Subcommittee.

IBD-A

- 12.12. The Committee considered that joint involvement is a frequent extra-intestinal manifestation of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC) with articular manifestations observed in approximately one third of patients with IBD. Members considered that arthralgias and spondyloarthritis in IBD patients were associated with considerable functional impairment, as well as disability and that axial involvement may vary from chronic inflammatory back pain, symptomatic or asymptomatic sacroiliitis to ankylosing spondylitis (AS). Members considered that up to 10% of patients with IBD would fulfil the criteria for a diagnosis of ankylosing spondylitis.
- 12.13. The Committee considered that there was limited evidence for the use of TNFs for IBD-A and most of it had been extrapolated from studies of TNF-alpha inhibitors for ankylosing spondylitis. Members considered that the best evidence for the use of TNFs in IBD-A comprised an open label, non-randomised, cohort study (CARE study, Löfberg et

al..Inflamm Bowel Dis. 2012 ;18:1-9)) which evaluated the clinical effectiveness (resolution of extra-intestinal manifestations) and safety of adalimumab in 945 pan-European patients with moderate to severe Crohn's disease. Patients received adalimumab induction therapy (160mg week 0, 80 mg week 2) followed by 40 mg every 2 weeks, dose adjustment to 40 mg weekly was permitted from week 12 onwards for non-response or disease flare.

- 12.14. Members noted that 497 (52%) of the patients enrolled had extraintestinal manifestations at baseline (445 (47%) had arthralgia, 82 (8.7%) arthritis and 50 (5.3%) had AS or Sacroiliitis). Members noted that of these 497 51% were free of signs and symptoms by week 20. However, members noted that week 20 assessments were not undertaken in all patients and considered that the imputation of last observation carried forward values may have the effect of over-estimating the benefit of adalimumab in this setting.
- 12.15. The Committee considered that adalimumab or infliximab were the preferred anti-TNF treatment options in patients with IBD-A as they would both also be beneficial for the underlying IBD. Members noted that although etanercept was not effective therapy for IBD itself there were a few case reports where it has shown some benefit for associated arthritis.
- 12.16. The Committee considered that the patient group likely to benefit from anti-TNF treatment were those patients with significant IBD-associated inflammatory arthritis. The Committee considered that PHARMAC staff's estimate of approximately 68 patients with IBD-A to be reasonable but expressed concern that widening of access may result in slippage to other non-indicated forms of arthritis/spondyloarthritis. Members considered it was important that patients' IBD diagnosis be made by a Gastroenterologist. Members considered that the proposed Special Authority criteria were not adequate as they were essentially PsA without SI joint involvement. Members considered that the criteria should include a defined level of disability (e.g. joint counts as for PsA) unless there was evidence that early treatment prevented joint destruction/disability in this setting.

13. Tacrolimus for nephrotic syndrome

Application

- 13.1. The Committee reviewed an application from a clinician for the funding of tacrolimus for the treatment of steroid and cyclosporin resistant nephrotic syndrome in children and in adults.

Recommendation

- 13.2. The Committee **recommended** that tacrolimus for steroid resistant nephrotic syndrome (SRNS) be funded in Section B of the Pharmaceutical Schedule with a high priority, subject to the following restrictions:

Initiation – steroid resistant nephrotic syndrome (SRNS)

Initial application only from a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Either

1. Patient is a child with SRNS where cyclosporin has been trialled in combination with prednisone and discontinued because of unacceptable side effects or inadequate clinical response; or
2. Patient is an adult with SRNS: and
 - 2.1 Both
 - 2.1.1 cyclosporin has been trialled in combination with prednisone and discontinued because of unacceptable side effects or inadequate clinical response; and
 - 2.1.2 either cyclophosphamide or mycophenolate have been trialled and discontinued because of unacceptable side effects or inadequate clinical response or the treatment is contraindicated.

- 13.3. The Committee **recommended** that PHARMAC seek advice from the relevant PTAC Subcommittees on further widening of access to tacrolimus for non-transplant indications if a price reduction occurs.
- 13.4. 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; 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

- 13.5. The Committee noted nephrotic syndrome is characterised by heavy proteinuria, hypoalbuminemia, and hyperlipidaemia; and the presentation and disease progression is different between children and adults.
- 13.6. The Committee considered the studies provided in support of the application were of low/moderate quality, small randomised controlled trials (RCTs) or non-experimental cohort studies, confirming overall good efficacy for tacrolimus in SRNS. The Committee noted no RCT looked at the efficacy of tacrolimus following cyclosporin failure in SRNS. The Committee considered in general the three RCTs were limited in strength and power of conclusions due to small patient numbers and a lack of long-term follow-up focusing on end stage renal disease (ESRD), which the Committee considered was a key end-point.
- 13.7. The Committee noted that Choudhry et al. (American J Kidney Disease 2009;53):760-9) conducted an open labelled, single centre, RCT of tacrolimus compared to cyclosporin in 41 paediatric patients with idiopathic SRNS receiving co-treatment with alternative day prednisolone and enalapril for 12 months. Relapse was greater in cyclosporin group (relative risk (RR), 4.5; 95% confidence interval (CI), 1.1 to 18; P=0.01), as were cosmetic adverse effects (hypertrochosis 95% vs. 0%, gingival hyperplasia 60% vs. 5%, p<0.001). Persistent nephrotoxicity was seen in 4.7% in the tacrolimus group vs. 10% in those taking cyclosporin.
- 13.8. The Committee noted the results from a number of small retrospective and prospective cohort studies: Bhimma et al (Am J Nephrol 2006; 26:544-51), Gulati et al (Nephrol Dial Transplant 2008;23:910-3), Wang et al (Ped Nephrol 2012;27:2073-79), Roberti et al (Ped Nephrol 2010;25:1117-24), Chen et al (Am J Med Sciences 2013;345(:81-7), Loeffler et al (Ped Nephrol 2004;19:281-7), Segarra et al (Nephrol Dial Transplant 2002;17:655-62). Members noted these studies included patients who have tried at least one previous immunosuppressive therapy. The Committee noted tacrolimus may induce remission in patients who have failed other therapies.
- 13.9. The Committee noted tacrolimus and cyclosporin are both calcineurin inhibitors. The Committee noted the mechanism for tacrolimus in nephrotic syndrome is not completely clear; however, tacrolimus may work in cyclosporin resistant patients due to better inhibition of vascular permeability factor in patients with minimal change disease and better cytokine suppression. The Committee considered the available evidence suggests tacrolimus is associated with minimal cosmetic adverse events compared with cyclosporin and lower risk of hypertension and dyslipidaemia, although greater risk of diabetes mellitus and neurotoxicity. The Committee noted a difference in adverse effects may help compliance.
- 13.10. The Committee noted the Kidney Disease Improving Global Outcomes International consensus recommendations (Eknoyan et al, Kidney International Supp. 2012;2:2) suggest a calcineurin inhibitor for 6 months, with concurrent low dose steroids is the first-line treatment for SRNS in children. Cyclophosphamide is not recommended on the basis of two small RCTs of cyclophosphamide and prednisolone, versus prednisolone, showing no difference in remission rates. The Committee noted in adults the treatment recommendations are different. In adult patients with minimal change disease,

cyclophosphamide is recommended before a calcineurin inhibitor. Members noted the authors comment that further RCTs are required to clarify which of cyclosporin or tacrolimus is preferred. In adults with focal segmental glomerulosclerosis (FSGS), cyclosporin is second-line after steroids and before mycophenolate. Members noted no RCTs have looked at tacrolimus for FSGS.

- 13.11. The Committee considered use of cyclophosphamide is limited in females of childbearing potential due to the impact on fertility.
- 13.12. The Committee considered the evidence for mycophenolate in SRNS is mainly in children and suggests that mycophenolate has less efficacy compared to tacrolimus. The Committee noted three non-experimental cohort studies of mycophenolate in SRNS, including patients who had previously failed to respond to cyclosporin. The Committee noted the current mycophenolate Special Authority criteria may preclude its funding in SRNS patients since this patient group is unlikely to be treated with azathioprine. The Committee noted the current rituximab Special Authority criteria would also preclude its use in SRNS.
- 13.13. The Committee noted the treatment algorithm provided with the application indicates rituximab treatment in SRNS would be considered after the use of cyclosporin and tacrolimus if this was available. The Committee considered the number of patients who may require rituximab would be low and funding applications could be made via the NPPA policy.
- 13.14. The Committee noted patients who do not respond to treatment may progress to ESRD and that dialysis is not easily accessible for rural patients. Members noted there is no clear evidence determining the proportion of patients with SRNS that would avoid ESRD if they were treated with tacrolimus. Studies reported the secondary end-point of complete or partial remission rather than avoidance of ESRD and limited follow-up date is available past 12 months of treatment. Members noted patients would benefit from tacrolimus treatment even if they did not achieve complete remission and treatment would likely continue in this situation. The Committee considered an estimate would be around 50% of patients would progress to ESRD and therefore require dialysis or transplantation. The Committee noted the reported survival rate of children with ESRD requiring renal replacement therapy was 79% at 10 years and 66% at 20 years, and mortality rates were 30 times as high as for children without ESRD (McDonald SP et al. NEJM. 2004;350:2654-62).
- 13.15. The Committee noted the cost effectiveness analysis produced by PHARMAC staff assumes 40kg for a child and this may be too high. Members noted the dose varies and younger children may require higher mg/kg doses to achieve the same target levels and a lower weight would improve cost effectiveness. Members noted that assessment of treatment costs for patients who develop ESRD should also include costs of renal transplantation, particularly in children.
- 13.16. The Committee considered the patient population that would benefit most were those patients with SRNS who have not responded to or are intolerant of cyclosporin. Members noted the NZ study by Wong (J Paed Child Health. 2007;43:337-41) provided an incidence of 1.9/100,000 of nephrotic syndrome in children aged 3 months to 15 years, 20% of which are steroid resistant. Members noted primary nephrotic syndrome is less prevalent in adults and incidence is unclear. The Committee considered an estimate of how many patients that would require tacrolimus for SRNS who have not responded to cyclosporin would be 10 to 15 children and adults per year. Members noted this may in fact be an overestimate and the risk of use in a high number of patients is low.
- 13.17. The Committee considered that access to tacrolimus for nephrotic syndrome should be restricted via Special Authority restriction to minimise financial risk. The Committee considered that it would be appropriate for tacrolimus to be restricted to children with SRNS to patients who have not responded to or are intolerant of cyclosporin. The Committee considered that in adults with SRNS tacrolimus be restricted to patients who have not responded to cyclosporin and also one of cyclophosphamide or mycophenolate, unless contraindicated. The Committee qualified these different recommendations by the pathology and the natural history of the disease in children and in adults.

- 13.18. The Committee considered the restrictions for tacrolimus should be reviewed if the price of tacrolimus capsules was significantly reduced and costs were more comparable to other immunosuppressant treatments. Members noted there have been a number of NPPA approvals for tacrolimus for non-transplant indications and removing the Special Authority restriction for tacrolimus would still likely be associated with a fiscal risk. The Committee noted that one option would be to list tacrolimus with no indication restriction for non-transplant indications and instead restrict it to any patient who has failed treatment with cyclosporin; however, PHARMAC staff would need to assess the financial risk associated with doing this. The Special Authority restriction for transplant patients would remain unchanged to allow tacrolimus to be used first-line in this patient group.

14. Tinzaparin

Application

- 14.1. The Committee reviewed an application from a clinician for the inclusion of tinzaparin on the Hospital Medicines List (HML, Part II of Section H of the Pharmaceutical Schedule)

Recommendation

- 14.2. The Committee **recommended** that tinzaparin not be listed on the HML.
- 14.3. The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals 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

- 14.4. The Committee noted that this application has been reviewed by the Haematology Subcommittee at its meeting in November 2013 and that the Subcommittee had recommended that tinzaparin not be listed on the HML. The Committee also noted the correspondence received from the applicant responding to the Haematology Subcommittee minutes. The Committee noted that the applicant considers that tinzaparin is preferred over other low molecular weight heparins (LMWHs) in pregnancy and cancer because of prospective clinical trial data in those settings and it can be used as a once-daily dose. The applicant also notes that the relevant datasheets highlight that tinzaparin has a B1 pregnancy category whilst enoxaparin is a category C treatment.
- 14.5. The Committee reviewed the clinical evidence relating to tinzaparin use in pregnancy and cancer. The Committee considered the strength of the clinical evidence for tinzaparin in pregnancy to be weak, consisting mainly of retrospective case reports with no controls, and the quality of that evidence to be poor with a high risk of bias. The Committee considered the strength and quality of the clinical evidence for tinzaparin in cancer to be moderate. The Committee considered that overall, the evidence presented did not indicate advantages of one LMWH over another in the setting of pregnancy or cancer.
- 14.6. The Committee also noted that similar number of patients on the three agents have been evaluated in systematic reviews, with no convincing argument to select one agent over another. The Committee noted that the Australian and New Zealand recommendations for the prevention of pregnancy-associated venous thromboembolism (VTE) (McLintock et al. ANZJOG. 2012;52:3-13) do not recommend one LMWH over another in pregnancy but it does recommend once daily dosing of tinzaparin when used in VTE treatment. The Committee noted however that enoxaparin is often dosed once daily in New Zealand clinical practice.
- 14.7. The Committee considered that the available clinical evidence did not indicate a clear difference between the pharmacokinetic profiles of the LMWHs, although the Committee noted that there were no direct comparisons. The Committee considered that there was no evidence to support that tinzaparin resulted in improved clinical outcomes when compared to the other LMWHs. The Committee noted that tinzaparin is not specifically

indicated in pregnancy according to its Medsafe datasheet and the recommended dosage in pregnancy is not detailed.

- 14.8. The Committee considered that based on the available evidence, for the purpose of comparing treatment costs, enoxaparin 40mg once daily (OD) is dose-equivalent to dalteparin 5000u OD and tinzaparin 4500u OD. The Committee considered that enoxaparin 40mg twice daily (BD) is dose equivalent to dalteparin 5000u BD and tinzaparin 10,500u OD. The Committee noted that, at current pricing, tinzaparin was more expensive than the other LMWHs.
- 14.9. The Committee noted that enoxaparin and dalteparin are currently listed on the Pharmaceutical Schedule. The Committee noted there may be clinical risks associated with listing another LMWH on the Pharmaceutical Schedule as highlighted by the Haematology Subcommittee. The Committee also noted that anticoagulation in pregnancy is increasingly being managed by general practitioners so the risk is not confined to the hospital setting. The Committee noted that the risks could potentially be mitigated through the development of clinical protocols.
- 14.10. The Committee noted that tinzaparin use is currently confined to one DHB and that DHB has instigated protocols for its use as well as having clinical experience using the product. The Committee noted that if tinzaparin were listed on the HML, other DHBs would not be able to prevent their clinicians from using tinzaparin if it were prescribed, who may not have the same experience as the clinicians in that one current DHB. The Committee noted that other DHBs would need to develop protocols and train their staff to manage the risks associated with having three LMWHs in the hospital with different dosages and dosing regimens.
- 14.11. The Committee **recommended** that tinzaparin not be listed on the HML. The Committee acknowledged that this recommendation would have a significant impact on the DHB whose clinicians currently prescribe tinzaparin. The Committee however considered that its recommendation was in line with the purpose of the HML, which is to improve the consistency of available treatments between DHBs. The Committee considered that although the relevant Medsafe datasheets indicate that tinzaparin could be safer in pregnancy when compared with the other LMWHs, its recommendation was consistent with current New Zealand and international guidelines. The Committee also noted that controlled switching from tinzaparin for patients in one DHB may be safer than exposing patients in the nineteen other DHBs to a new LMWH whose clinicians have little clinical experience with this, with the potential for error exacerbated by LMWH differing dosages and dosing regimens in these DHBs; this factor alone would not justify listing a medicine appreciably more expensive than currently funded LMWHs.

15. Glycopyrronium bromide for management of COPD

Application

- 15.1. The Committee reviewed an application from Novartis for the inclusion of glycopyrronium bromide on the Pharmaceutical Schedule for the treatment of chronic obstructive pulmonary disease.

Recommendation

- 15.2. The Committee **recommended** that glycopyrronium bromide be listed on the Pharmaceutical Schedule under the same Special Authority criteria, but only if it is cost-neutral to tiotropium.
- 15.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori 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.

Discussion

- 15.4. The Committee noted that glycopyrronium bromide is an inhaled long-acting muscarinic receptor antagonist (LAMA) indicated as a once-daily maintenance bronchodilator in chronic obstructive pulmonary disease (COPD). The Committee noted that glycopyrronium bromide is a high affinity muscarinic receptor antagonist of subtypes M1-3 that has a rapid onset of action.
- 15.5. The Committee noted that COPD is a major cause of disability, hospital admission and premature death worldwide with prevalence increasing with age and, in most countries, it is more prevalent in men. The Committee noted that in New Zealand the prevalence of COPD is between 6.5 to 5%, with higher rates reported for Māori of between 12.9 to 3.1%. Māori are 3 to 4 times more likely to be hospitalised, 5 times more likely to die from COPD-related causes and are affected at a younger age than their European counterparts.
- 15.6. The Committee noted that Novartis had supplied three phase III trials that provided the main evidence of glycopyrronium bromide in the treatment of COPD (GLOW 1, GLOW 2 and GLOW 3) and a phase II study (A2207).
- 15.7. The Committee noted that D'Urzo et al studied the efficacy and safety of once-daily glycopyrronium bromide in patients with moderate to severe COPD: the GLOW 1 trial (Respir Res 2011;12:156-169). This was a 26 week, placebo controlled trial with 822 enrolled patients randomised to glycopyrronium bromide or placebo. Patients ceased taking long acting bronchodilator therapy with a two day washout for LABAs/ICS and a 7 day wash out for tiotropium. Rescue medication was supplied in the form of salbutamol/albuterol inhalers. The primary end point was trough FEV1 at week 12, secondary endpoints were breathlessness on the transition dyspnoea index (TDI) and health related quality of life (HRQoL) according to the St George's Respiratory Questionnaire (SGRQ) at week 26. Least squares mean trough at week 12 was significantly higher in patient receiving glycopyrronium bromide and significant improvements in trough FEV1 were apparent at the end of Day 1 and sustained through week 26. TDI scores and SGRQ scores were significantly improved at week 26 versus placebo. Glycopyrronium bromide was well tolerated with an acceptable safety profile, with low frequency of cardiac and typical antimuscarinic side effects.
- 15.8. The Committee noted that Kerwin et al. also studied the efficacy and safety of once daily glycopyrronium bromide in patients with moderate to severe COPD: the GLOW 2 trial (Eur Respir J. 2012; 40(5):1106-1114). This was a 52 week open-label study with 1066 patients randomised to receive glycopyrronium bromide, tiotropium or placebo. The design was similar to GLOW 1 with the same primary and secondary outcomes. At week 12, trough FEV1 increased significantly by 97 mL with glycopyrronium bromide, and 93 mL with tiotropium compared to placebo. At the end of day 1, week 26 and week 52 trough FEV1 significantly favoured glycopyrronium bromide and tiotropium. Compared to placebo, glycopyrronium bromide produced significant improvements in dyspnoea (TDI) at week 26 and health status (SGRQ) at week 52. Serial spirometry in a subpopulation of patients demonstrated that glycopyrronium bromide provided rapid bronchodilation following the first dose on Day 1, with significantly higher FEV1 points from 5 min to 4 hours post-dose compared to placebo and tiotropium. Glycopyrronium bromide was well tolerated with a safety profile similar to placebo and tiotropium.
- 15.9. The Committee noted that GLOW 3 (Beeh et al. Int J Chron Obstruct Pulmon Dis. 2012;7:503-513) was a small 21 day trial with 108 patients randomised to glycopyrronium bromide or placebo. The primary endpoint was endurance time during an ergometry test on day 21. Glycopyrronium bromide was superior to placebo after three weeks of treatment with a least squares mean (LSM) treatment difference of ~89 seconds, being a 21% improvement compared with placebo. The treatment difference at day 1 was also significant with an LSM difference of 43.1 sec, ~10% improvement compared with placebo.

- 15.10. The Committee noted two further studies examining glycopyrronium bromide in combination with indacaterol that were not relevant to this application.
- 15.11. The Committee noted there were 14 studies comprising over 3,500 patients that have contributed to safety knowledge, with ~2,500 receiving glycopyrronium bromide monotherapy. Overall the safety profile appeared to be good, with most reported adverse events being disease-related and the overall incidence of adverse reactions, stratified by organ system, being similar to placebo. Treatment related anticholinergic adverse events in glycopyrronium bromide patients were 5.8% (similar to tiotropium at 6%) and included dry mouth (2.2%); worsening of symptoms associated with benign prostatic hyperplasia (0.3%) and glaucoma in one patient.
- 15.12. The Committee considered the strength and quality of the evidence provided by the supplier was level 1+ (well-conducted RCTs with a low risk of bias), indicating that glycopyrronium bromide to be better than placebo as a bronchodilator and comparable to tiotropium, with level 1 evidence of similar safety to placebo and tiotropium.
- 15.13. The Committee considered glycopyrronium bromide has the same or similar effect as tiotropium 18 mcg. The Committee noted some concern that in some of the studies glycopyrronium bromide was used twice-daily as opposed to once-daily tiotropium, and that recommending twice daily use may become the default promotion by the supplier which could have significant financial effects. The Committee considered that, overall there was no additional health benefit versus tiotropium other than possibly a more rapid onset. The Committee noted some concern regarding safety in that the trials to date have been short and there have been no studies of compliance.
- 15.14. The Committee **recommended** listing glycopyrronium bromide on the Pharmaceutical Schedule under the same Special Authority criteria as tiotropium and only if cost-neutral to tiotropium 18 mcg per day.