

**PTAC meeting held on 13 & 14 August 2015**  
**(minutes for web publishing)**

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

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## 1. Correspondence / Matters Arising

### ***Nab-paclitaxel for metastatic adenocarcinoma of the pancreas***

- 1.1. The Committee noted a funding application from the New Zealand Gastrointestinal Cancer Special Interest Group for the funding of nab-paclitaxel for adult patients with unresectable adenocarcinoma pancreas - ECOG 0-3, including older adults. The Committee noted that it had previously considered the evidence provided with the application at its February 2015 meeting.
- 1.2. The Committee noted a letter and additional references from the supplier of nab-paclitaxel, Specialised Therapeutics Limited, in response to PTAC's February 2015 minute. Members considered that the evidence supporting the majority of points made in the letter was of poor quality. Further, the Committee noted that some points did not properly reflect PTAC's view. The Committee considered that although it remained concerned about the overall benefits, risks and costs of nab-paclitaxel, that it was reasonable to change its recommendation in order to enable PHARMAC to negotiate further with its supplier on price.
- 1.3. The Committee **recommended** that nab-paclitaxel (Abraxane) in combination with gemcitabine should be funded, with low priority, for the first-line treatment of metastatic adenocarcinoma of the pancreas.
- 1.4. 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 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.*

### ***Buprenorphine sublingual tablets***

- 1.5. The Committee noted correspondence from a clinician regarding PTAC's February 2015 recommendation to decline a funding application for buprenorphine sublingual tablets (Subutex) for women who are stabilised on buprenorphine with naloxone sublingual tablets (Suboxone) and then become pregnant. The Committee noted that the clinician was seeking clarification on what treatment was appropriate in this situation.
- 1.6. The Committee noted that, as with any clinical situation, clinicians must weigh up the benefits and risks of the treatments available to them when determining the most appropriate treatment for their patients. The Committee noted that there are two registered pharmaceuticals for the treatment of opioid addiction in New Zealand, methadone and Suboxone, and that these were the treatments clinicians could consider for their patients.
- 1.7. The Committee noted that buprenorphine sublingual tablets are not registered for use in New Zealand and have never had an indication for use in pregnancy. The Committee noted that it could reconsider an application for the funding of Subutex if it should gain registration in New Zealand.

### ***Aflibercept for wet age-related macular degeneration***

#### *Letter from Bayer New Zealand Ltd*

- 1.8. The Committee noted correspondence from Bayer in response to PTAC's February 2015 meeting minutes for aflibercept in treatment of wet age-related macular degeneration (wAMD).

- 1.9. The Committee considered the information provided does not change its previous recommendation to run a competitive process for a second line anti-vascular endothelial growth factor (anti-VEGF) treatment of wAMD following bevacizumab treatment. Members also noted that a recommendation on a possible listing of a third line agent would be dependent on the outcome of the competitive process.

*Letter from two members of the Ophthalmology Subcommittee*

- 1.10. The Committee noted correspondence from two members of the Ophthalmology Subcommittee of PTAC regarding aflibercept.
- 1.11. The Committee noted that each agent had its own advantages which could affect treatment costs and healthcare resource utilisation. The Committee considered these differences would be taken into account in any future decision regarding the outcome of a competitive process and this should be communicated to the Ophthalmology Subcommittee. The Committee **recommended** PHARMAC progress with the competitive process as there is a significant fiscal risk with these agents due to a very large patient group size. Members noted that they have taken all information provided into consideration and would like to see the outcome of the competitive process before making any recommendation on the funding of a third line anti-VEGF agent for wAMD .

**Benzbromarone**

- 1.12. The Committee noted information from Te Arai BioFarma in relation to the funding of benzbromarone. The Committee noted that it had recently recommended changes to the benzbromarone funding criteria (in February 2015) and the Committee considered that no further changes were necessary at this time.

**Bart's Solution**

- 1.13. The Committee reiterated its May 2015 **recommendation** that the 1000 ml presentation of glucose 4% with sodium chloride 0.18% solution ("Bart's solution") is listed in Part II of Section H of the Pharmaceutical Schedule.
- 1.14. The Committee **recommended** that a restriction be placed on this item limiting its use to adults.
- 1.15. The Committee **recommended** that a note be inserted on this item advising of the strong evidence of a significant increase in potentially life-threatening hyponatremia with its use.
- 1.16. 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.*
- 1.17. The Committee noted its earlier recommendation to refer the safety concerns raised during consultation on the listing of Bart's solution to the Medicines Adverse Reactions Committee (MARC) at Medsafe for its review.
- 1.18. The Committee noted the letter received from Associate Professor David Reith, MARC Chair dated 12 August 2015. This letter advised that MARC provides expert advice on medical and scientific evaluations of medicines safety issues referred to the MARC by Medsafe. Medsafe have advised MARC that they will review this safety concern. The Committee noted further correspondence between PHARMAC staff and Medsafe, noting that this review should be completed within 12 months.

**2. Subcommittee Minutes**

***Transplant Immunosuppressant Subcommittee, May 2015***

- 2.1. The Committee noted and accepted the minutes from the Transplant Immunosuppressant Subcommittee meeting of 11 May 2015.

#### ***Diabetes Subcommittee Minutes, April 2015***

- 2.2. The Committee noted the record of the Diabetes Subcommittee meeting held on 16 April 2015.
- 2.3. The Committee accepted the recommendations in paragraphs 1.1 to 8.5 and 8.7 to 9.2
- 2.4. In relation to section 8, the Committee noted that the review of applications for insulin pumps and consumables will undergo a transition from the Insulin Pump Panel to a Special Authority. The Committee noted paragraph 8.6 - the Special Authority for insulin pumps and consumables and considered the renewal criteria for insulin pump consumables. The Committee noted that the criteria may not allow flexibility for patients who nearly meet these but considered that PHARMAC has the ability to review these renewal applications on a case by case basis.

#### ***Mental Health Subcommittee minutes, June 2015***

- 2.5. The Committee noted and accepted the minutes from the Mental Health Subcommittee meeting of 4 June 2015.

#### ***Respiratory Subcommittee minutes***

- 2.6. The Committee noted the record of the Respiratory Subcommittee meeting held on 4 March 2015.
- 2.7. The Committee accepted the recommendations from 1.1 to 4.38 and 4.41 to 7.10.
- 2.8. In relation to dornase alfa, the Committee agreed with the removal of the six month FEV<sub>1</sub> improvement criteria. With respect to widening access to treatment to all patients with cystic fibrosis under the age of six years the Committee asked to review the clinical evidence to support this and also review the likely costs associated with this change. The Committee also requested the Respiratory Subcommittee develop draft criteria for access to dornase alfa for this age group. The Committee asked for this information to be presented at its November 2015 meeting.
- 2.9. In relation to COPD treatments, the Committee reiterated that the diagnosis of COPD must include diagnosed by spirometry. The Committee noted that FEV<sub>1</sub> levels are not strongly related to quality of life but had been used in the Special Authority for tiotropium so that this treatment was more likely to be used in a patient group similar to the RCT's that support its use. The Committee noted that FEV<sub>1</sub> may not be useful to guide use of inhaled agents for COPD. The Committee considered that open listing the long-acting muscarinic-agents may be appropriate if the cost of these agents was lower.

### **3. Amino Acid Formula and Extensively Hydrolysed Formula**

- 3.1. The Committee noted the Special Foods Subcommittee had recommended that PTAC consider a rapid paper highlighting issues, regarding expenditure and prescribing volumes of infant formula, identified during its 22 July 2015 meeting.

#### **Discussion**

- 3.2. The Committee considered the minutes of the discussion on Amino Acid and Extensively Hydrolysed Infant Formulas from the Special Foods Subcommittee meeting held on 22 July 2015, and noted and accepted the Subcommittee's recommendations as detailed below:
- 3.3. The Subcommittee **recommended** that PHARMAC establish a Clinical Panel to review initial applications for these Infant Formula preparations for children over 12 months of

age and renewals for all children over 12 months of age. The Subcommittee noted although there is a cost associated with setting up the Panel, overall this approach may lead to prescribing that is more closely aligned with the current Special Authority criteria and should be cost-effective.

- 3.4. The Subcommittee **recommended** PHARMAC provide educational support for prescribers in primary and secondary care to improve prescribing practice.
- 3.5. The Subcommittee **recommended** another audit of high-use prescribers after first communicating an appropriate penalty for not following the Special Authority criteria. In addition, correspondence to other clinicians such as general practitioners and community dietitian prescribers should be included within the scope of the audit to determine whether responsibilities are being transferred onto other prescribers.
- 3.6. The Subcommittee **recommended** amending the SA1380 criteria for initial applications for extensively hydrolysed formula to include an additional criterion of 'Step down from funded amino acid formula' to ensure the pathway was in place to allow children receiving amino acid formula to be transferred to extensively hydrolysed formula.
- 3.7. The Subcommittee **recommended** submitting a late paper to the August 2015 PTAC meeting to show the PTAC members data on infant formula being used for patients over 12 months.
- 3.8. The Committee noted that the remainder of the record of the Special Foods Subcommittee meeting on 22 July 2015 would be reviewed at the Committee's next meeting.

#### **4. Cannabidiol with tetrahydrocannabinol (Sativex) for spasticity due to multiple sclerosis, pain (including pain associated with spasticity) and treatment-refractory epilepsy**

##### **Application**

- 4.1. The Committee considered a paper from PHARMAC staff considering the funding of cannabidiol with tetrahydrocannabinol (Sativex) for spasticity due to multiple sclerosis, pain (including pain associated with spasticity) and treatment-refractory epilepsy.

##### **Recommendation**

- 4.2. The Committee **recommended** that funding for cannabidiol with tetrahydrocannabinol (Sativex) for spasticity due to multiple sclerosis be declined.
- 4.3. The Committee **recommended** that funding for cannabidiol with tetrahydrocannabinol (Sativex) for pain, including pain associated with spasticity, be declined.
- 4.4. The Committee **recommended** that funding for cannabidiol with tetrahydrocannabinol (Sativex) for treatment-refractory epilepsy be declined.
- 4.5. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health service users.*

##### **Discussion**

- 4.6. The Committee noted that cannabidiol with tetrahydrocannabinol (Sativex) is formulated as a solution for oromucosal use and comes in a 10 ml spray container. The Committee noted that each ml contains: 38-44 mg and 45-42 mg of two extracts from *Cannabis sativa* L., folium cum flore (cannabis leaf and flower) corresponding to 27 mg delta-9-

tetrahydrocannabinol and 25 mg cannabidiol, with each 100 microlitre spray containing 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD). The Committee considered that the combination may also be referred to as nabiximols.

- 4.7. The Committee noted that, because it is a cannabis preparation, Sativex, is classified as a Schedule 2 Class B(1) drug product under the Misuse of Drugs Act 1975. The Committee noted that Ministerial approval is required before Sativex can be prescribed by a New Zealand registered medical practitioner, for any use, under regulation 22 of the Misuse of Drugs Regulations 1977.
- 4.8. The Committee noted that cannabidiol with tetrahydrocannabinol (Sativex) is registered as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. The Committee noted that the recommended maximum dose is 12 sprays per day, but considered that, due to the inter-patient variability in pharmacokinetics with cannabidiol with tetrahydrocannabinol, dosing requirements would vary between patients.
- 4.9. The Committee noted that tetrahydrocannabinol acts as a partial agonist at both CB1 and CB2 cannabinoid receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters; however, the exact mechanism of action of cannabidiol is not fully understood.
- 4.10. The Committee considered that the risk of diversion in the New Zealand setting should Sativex be funded is high due to the inherent nature of its active substances and the ease of administration.

### **Spasticity due to multiple sclerosis**

- 4.11. The Committee noted that there are approximately 2500 people with MS in New Zealand. The Committee noted that spasticity can affect the gait of a person with MS. The Committee noted that spasm and spasticity are common symptoms affecting up to 80% of people with MS and that moderate (defined as: frequently affects activities), severe (forced to modify activities daily) or total spasticity (prevents daily activities) are reported to affect around 34% of people with MS. (Rizo et al. *Mult Scler* 2004, 10:589-95).
- 4.12. The Committee noted that there are a number of funded treatments in the community for the treatment of spasticity, including baclofen, dantrolene, orphenadrine and benzodiazepines and, in addition, botulinum toxin injections are listed on the Hospital Medicines List.
- 4.13. The Committee noted that PHARMAC had received two Named Patient Pharmaceutical Applications (NPPA) for Sativex for the treatment of spasticity due to MS and that both applications were withdrawn as the pre-requisites of the NPPA policy were not met.
- 4.14. The Committee considered the CAMS study reported by Zajicek et al. (*Lancet* 2003;362:17-1526); a 15 week, randomised, multicentre, placebo-controlled trial investigating cannabinoids for treatment of spasticity and other symptoms related to MS. A total of 657 patients with MS and muscle spasticity were randomised to receive treatment with either oral cannabis extract (n = 219), delta-9-tetrahydrocannabinol (n=216), or placebo (n=222). Analysis was by intention to treat and data were obtained for 611 patients; cannabis extract (n=207), delta-9-tetrahydrocannabinol (n=197) and placebo (n=207). The Committee noted that the primary outcome measure of the trial was change in spasticity scores, using the Ashworth scale. The Committee noted that the authors reported no treatment effect of cannabinoids on the primary outcome (p=0.40); the estimated difference in mean reduction in total Ashworth score for patients

taking cannabis extract compared with placebo was 0.32 (95% CI -1.04 to 1.67), and for those taking delta-9-tetrahydrocannabinol versus placebo it was 0.94 (-0.44 to 2.31).

- 4.15. The Committee considered a double blind, randomised, parallel group, placebo controlled trial of a combination of delta-9-tetrahydrocannabinol and cannabidiol in patients with MS (Wade et al. *Mult Scler* 2004;10:434-41). A total of 160 patients with MS experiencing problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain were randomised to either an oromucosal spray containing placebo or a cannabis-based medicinal extract (CMBE) containing equal amount of THC and cannabidiol at a dose of 2.5-120 mg (1-48 sprays) of each daily, in divided doses for six weeks. The primary outcome, after four weeks, was a Visual Analogue Scale (VAS) for each patient's most troublesome symptom; termed as the Primary Symptom Score (PSS). The Committee noted that no statistically significant difference between the groups was reported for the PSS; the PSS reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CMBE and from 74.31 (12.5) to 54.79 (26.3) following placebo (P = 0.124). The Committee noted that the authors reported that patients on active treatment whose primary symptom had been spasticity showed a significant reduction in their VAS comparison with placebo; patients treated with CMBE had an average difference in VAS improvement compared with the placebo group of 22.79 [95% CI -35.52, -10.07], (P=0.001). The Committee noted that the adverse effects associated with the use of CBME were reported to be generally mild.
- 4.16. The Committee considered an open-label extension trial of the trial described in the previous paragraph. (Wade et al. *Mult Scler* 2006;12:639-45). The Committee noted that in this long-term follow-up (up to 82 weeks) involving 137 patients, that a total of 58 patients (42.3%) withdrew due to: lack of efficacy (n=24); adverse events (n=7); withdrew consent (n=6); lost to follow up (n=3); and other (n=8). The Committee noted that the majority of adverse events were reported as mild, however, five had 'serious adverse events' between them – two seizures, one fall, one aspiration pneumonia and one gastroenteritis and that four patients were reported to have first-ever seizures.
- 4.17. The Committee considered a randomised controlled double blind study reported by Colin et al. (*Eur J Neurol* 2007;14:290-6). A total of 189 patients were randomised in a 2:1 ratio to receive either Sativex (n=124) or placebo (n=65) for a 6 week period. The Committee noted that the primary outcome measure was the Ashworth Scale but publication of the CAMS trial, which used the Ashworth Scale as the primary outcome measure, did not demonstrate a beneficial effect on spasticity, therefore the authors of this trial changed the primary outcome to be change in Numerical Rating Scale (NRS) of spasticity. The Committee noted that patients were instructed to titrate their doses to a maximum of 48 sprays per day. The Committee noted that the adjusted mean change in NRS spasticity scores for the Sativex treatment at the end of treatment was reported to show a reduction of 1.18 points (from a mean baseline score of 5.49) compared with the placebo group that showed a reduction of 0.63 points (from a mean baseline score of 5.39); the difference in favour of Sativex was statistically significant (p=0.048; 95% CI: -1.029, -0.004 points).
- 4.18. The Committee considered a two phase, enrichment designed study of the safety and efficacy of Sativex as add-on treatment, in patients with refractory MS spasticity (Novotna et al. *Euro J Neurol* 2011;18:1112-31). A total of 572 patients were enrolled into a 4 week run-in phase, single blind treatment trial with Sativex to identify responders to treatment. Participants were blinded to whether they were taking placebo or treatment, however, investigators were aware that all participants were allocated to treatment with Sativex. The Committee noted that only responders (defined as those who achieved an improvement of >20% in spasticity, as measured by the NRS) then continued on to a 12 week randomised, placebo controlled phase. The Committee noted that of the 572 patients recruited in the initial run-in phase, 272 were reported to have achieved a >20% improvement in spasticity and 241 of these patients were then randomised to receive either Sativex (n=124) or placebo (n=117). The Committee noted

that the authors of the study reported that over the 12 week double-blind, randomised phase, the mean spasticity score improved in the Sativex group by 0.04 (from a baseline score of 3.87 points) and deteriorated in the placebo group by 0.81 (from a baseline score of 3.92 points); the difference between the groups was 0.84 points (95% CI: -1.29 to -0.40) (P=0.0002).

- 4.19. The Committee considered a double-blind, placebo controlled, crossover study reported by Aragona et al. (Clin Neuropharmacol 2009;32:41-7) that investigated possible psychopathological and cognitive effects as well as general tolerability, effects on quality of life, fatigue and motor function in patients treated by Sativex. The Committee noted that the authors of the trial reported that post-placebo versus post-cannabinoid scores showed that no significant differences could be detected on all the variables under study.
- 4.20. The Committee considered a meta-analysis investigating the efficacy and safety of Sativex on spasticity in people with MS (Wade et al. Mult Scler 2010;16:707-14). The Committee noted that the authors reported the adjusted mean change of the NRS from baseline in the Sativex group was -1.30 compared with -0.97 for placebo. The treatment difference was -0.32 (95% CI -0.61, -0.04; p=0.026). The Committee noted the high numbers of patients reported experiencing at least one adverse event; 288 (79.3%) of patients treated with nabiximols compared with 169 (55.8%) placebo patients. The Committee noted the most common adverse events occurring with nabiximols were nervous system disorders, gastrointestinal disorders, administration site reactions, psychiatric disorders, ear and labyrinth disorders and musculoskeletal and connective tissues disorders. The Committee noted that the most common adverse reaction in the nabiximols group was dizziness, in 32% of patients, compared with 11% of placebo patients and considered that in practice this could limit the usefulness of nabiximols for patients with spasticity and mobility difficulties.
- 4.21. The Committee considered a review reported by Lu et al. (Pharmacoeconomics 2012;30:1157-71) on the cost effectiveness of Sativex for spasticity in MS, in the United Kingdom. The Committee noted a Markov model was used and the population modelled were adults with moderate to severe spasticity due to MS who did not respond adequately to oral anti-spasticity medication. The Committee noted that the model did not include potential use of botulinum toxin injections as standard of care. The Committee noted the model chosen was a trial period of 4 weeks followed by ongoing treatment restricted to responders. The model assumed 58% of patients withdrew after a trial with 4% of the remaining patients withdrawing each month after a longer trial. The model chosen used a 5 year time horizon. The Committee noted the authors estimated a gain over 5 years of 0.15 QALYs at an incremental cost of £7,600, resulting in an incremental cost-effectiveness ratio of £49,000 per QALY.
- 4.22. The Committee noted the outcomes of reviews from the Pharmaceutical Benefits Advisory Committee of Australia, NICE of the United Kingdom and the All Wales Medicines Strategy Group.
- 4.23. The Committee noted that in the majority of the clinical trials Sativex was used as an adjunctive treatment and no trials compared Sativex as an adjunctive treatment to botulinum toxin injections, which the Committee considered are currently the standard of care for this group of patients in New Zealand. The Committee noted that in many of the clinical trials, doses of greater than 12 sprays per day were used and considered that, if Sativex was funded, this may also occur in clinical practice.
- 4.24. The Committee considered that the majority of outcome measures reported in the clinical trials were patient-reported and in view of the prominent other effects of this agent likely to contribute to a high risk of bias. The Committee noted that clinically relevant objective outcome measures, such as walking ability, were not reported. The

Committee considered that the effect size reported in favour of Sativex is of uncertain clinical significance.

- 4.25. Overall, the Committee considered that there was some evidence to support the use of Sativex for spasticity due to MS compared with placebo, but that the strength of this evidence was weak and the quality was poor.
- 4.26. The Committee considered that if Sativex was funded, it would be used as an add-on treatment to the currently funded treatments. In addition, the Committee considered that, due to the progressive nature of the disease, physiotherapy and mobility aids would still be needed. The Committee noted that it could identify no published evidence of any potential cost-offsets from the use of Sativex for the treatment of spasticity due to MS.
- 4.27. The Committee considered that PHARMAC's estimates for potential patient numbers were reasonable.
- 4.28. The Committee considered that there are several other conditions such as stroke, traumatic brain injury and cerebral palsy that are also associated spasticity; however, there did not appear to be sufficient published evidence at this time to warrant further investigation in these indications.
- 4.29. The Committee considered that moderate to severe spasticity due to MS would not be limited to patients with relapsing remitting multiple sclerosis and that patients with progressive MS would also be part of this group. The Committee considered that patients who have difficult to treat moderate to severe spasticity due to MS may, due to the nature of the disease, also have difficulties with mobility and cognitive function and be more susceptible to experiencing adverse events. The Committee considered that although adverse events in the trials were reported to be generally mild to moderate, it remained concerned regarding the potential for cognitive effects and other adverse events occurring in a vulnerable patient population.

#### **Pain, including pain associated with spasticity**

- 4.30. The Committee noted that PHARMAC had received six NPPA applications for Sativex for the treatment of pain, including pain associated with spasticity, five of which were withdrawn as the pre-requisites of the NPPA policy were not met and one application was declined.
- 4.31. The Committee considered that pain is common in advanced and progressive disease and noted that chronic pain can be difficult to treat.
- 4.32. The Committee noted that there are a large number of non-opioid and opioid analgesics, in various formulations, funded on the Pharmaceutical Schedule. The Committee noted that there are also a number of non-pharmacological treatments that are routinely used in the management of chronic pain, including physical and psychological therapies.
- 4.33. The Committee considered a randomised placebo-controlled graded-dose trial investigating the efficacy of nabiximols (Sativex), in opioid-treated patients with cancer and chronic pain (Portenay et al. *J Pain* 2012;13:438-9). A total of 360 patients with advanced cancer and opioid-refractory pain were randomised to receive placebo or Sativex at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day) for a duration of 5 weeks. Participants continued their scheduled opioid dose and were allowed to use their breakthrough opioids as needed. The Committee noted that the authors reported an improvement in sleep disturbance reported for the low dose group with a treatment difference of 0.88 points in favour of Sativex ( $p=0.003$  95% CI: 1.45, 0.31 points); however, the 30% responder rate primary endpoint was not significant for Sativex versus placebo ( $p=0.59$ ). The Committee noted that neither the use of regularly scheduled opioids nor the number of opioid doses taken as needed for breakthrough-pain was reported to vary significantly between treatment

groups. The Committee noted that the authors reported there was a dose-related incidence of adverse events, with the high-dose group comparing unfavourably with placebo and the two lower dose groups showing little difference from placebo.

- 4.34. The Committee considered a randomised placebo-controlled double blind trial investigating the efficacy of Sativex as an adjunctive treatment in painful diabetic peripheral neuropathy (Selvarajah et al. *Diabetes Care* 2010;33:128-30). The Committee noted that improvement in pain, as assessed by the pain diary and Neuropathic Pain scale (NPS) questionnaire, was used as the primary outcome measure and that secondary outcome measures were quality of life (QOL) assessed by McGill Pain and QOL, SF-36 Health Survey and EuroQOL questionnaires. The Committee considered that the authors reported there was significant improvement in pain scores in both groups, but mean change between groups was not significant. There were no significant differences in secondary outcome measures.
- 4.35. The Committee considered a double-blind, randomised, placebo-controlled, parallel-group trial of Sativex in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with MS (Langford et al. *J Neurol* 2013;260:984-97). Patients who had failed to gain adequate analgesia from existing medication were treated with Sativex or placebo as an add-on treatment in a double blind manner for 14 weeks. This parallel-group phase of the study was then followed by an 18 week randomised withdrawal study (14-week open-label treatment period plus a double-blind 4-week randomised-withdrawal phase) to investigate time to treatment failure and maintenance of efficacy. The Committee noted that 339 patients were randomised to phase A (167 received Sativex and 172 received placebo) and of those who completed phase A, 58 entered the randomised-withdrawal phase. The Committee noted that the primary endpoint of responder analysis at the 30% level at week 14 of phase A of the study was reported to not be met, with 50% of patients on Sativex classed as responders at the 30% level compared to 45% of patients on placebo ( $p=0.234$ ).
- 4.36. The Committee considered a multicentre, double-blind, randomised, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain (Johnson et al. *J Pain Symptom Manage* 2010;39:167-79). A total of 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week trial and were randomised to receive either THC:CBD extract ( $n=60$ ), THC extract ( $n=58$ ), or placebo ( $n=59$ ). The primary endpoint measure was the change from baseline in mean pain Numerical Rating Scale (NRS) score and that the authors reported the adjusted mean reduction in NRS for the THC:CBD, THC and placebo groups at the end of the treatment were -1.37, -1.01, and -0.69 points respectively. The Committee considered that the adjusted mean treatment difference from placebo was reported to be statistically significant for a reduction in pain with the THC:CBD extract (0.67 points,  $p=0.014$ ) but not the THC extract (0.32 points,  $p=0.245$ ). The Committee noted that no change from baseline was reported for the median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups.
- 4.37. The Committee considered a systematic review and meta-analysis of the benefits and adverse events of cannabinoids (Whiting et al. *JAMA* 2015; 313:2456-73). Randomised clinical trials of cannabinoids for the following indications were included: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDs, chronic pain (including neuropathic pain), spasticity due to MS or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma or Tourette syndrome. The Committee noted that the authors reported that most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with greater average number of patients showing complete nausea and vomiting response (47% vs 20%; OR, 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10

point scale; weighted mean difference, -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.36 [95% CI, -0.69 to -0.05]; 7 trials). The Committee noted that there were a large number of trials reported in the review to be at high risk of bias. The Committee noted the common adverse events reported in the review included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

- 4.38. The Committee considered that there is no available evidence to support the use of nabiximols (Sativex) for the treatment of acute pain.
- 4.39. The Committee considered that there are a large number of patients with non-malignant chronic pain that is resistant to currently available analgesic agents. Members also noted that, anecdotally, cannabis use appears to be relatively prevalent in patients attending chronic pain clinics. The Committee considered that non-pharmacological treatment, including psychological therapies and physical rehabilitation, is an important component of chronic pain management.
- 4.40. The Committee considered that if Sativex was funded for pain, including pain associated with spasticity, that potential patient numbers may be high.
- 4.41. The Committee noted that the majority of outcome measures reported in the clinical trials were patient-reported outcome measurements and may lead to a high risk of bias in the estimates differences between Sativex and placebo. The Committee noted that maximised standard of care did not appear to be the comparator in the majority of trials. The Committee considered that improving function, reduction in other analgesic medication use, and improving quality of life would be more clinically relevant outcome measures for the management of pain than subjective measures such as pain scores.
- 4.42. Overall, the Committee considered that the evidence to support the use of Sativex for pain, including pain associated with spasticity, was poor. The Committee considered that there was a risk that if Sativex was funded it may be used instead of more effective treatments with stronger evidence of effectiveness.

#### **Treatment-refractory epilepsy**

- 4.43. The Committee noted that PHARMAC had received three NPPA applications for Sativex for treatment-refractory epilepsy; two were withdrawn as the pre-requisites of the NPPA policy were not met and one application was declined.
- 4.44. The Committee noted that as many as 20% to 40% of patients with epilepsy are estimated to have treatment-refractory epilepsy, and these patients also have the greatest burden of epilepsy-related disabilities and a high health need.
- 4.45. The Committee noted that there is a large range of funded anti-epilepsy treatments but that there would always be a small proportion of patients who continue to have seizures despite having tried all suitable funded options.
- 4.46. The Committee considered that PHARMAC's estimates for potential patient numbers were reasonable.
- 4.47. The Committee noted that there are anecdotal reports of the use of cannabinoids for the treatment of epilepsy; however, no controlled trials have been published to support the use of cannabidiol with tetrahydrocannabinol (Sativex) for treatment-refractory epilepsy.
- 4.48. The Committee considered a Cochrane review (Vickrey and Gloss. Cochrane Database Syst Rev. 2014 Mar 5;3:CD009270) that assessed the efficacy and safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy. The primary outcome investigated was seizure freedom at one year or more, or three

times the longest interseizure interval. Secondary outcomes included responder rate at six months or more, objective quality of life data, and adverse events. The Committee noted that the authors identified reports for four randomised trials that included a total of 48 patients, each of which used cannabidiol as the treatment agent and antiepileptic drugs were continued in all studies. One report was an abstract and another was journal correspondence published as a letter. The Committee noted that the authors had concluded that no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy and that further trials are needed.

- 4.49. The Committee considered that the strength and quality of evidence to support the use of cannabidiol with tetrahydrocannabinol (Sativex) for the treatment of epilepsy and seizures was poor.

## 5. Febuxostat (Adenuric) for the treatment of gout

### Application

- 5.1. The Committee considered an application from Te Arai BioFarma to widen funded access to febuxostat (Adenuric) for the treatment of gout.

### Recommendation

- 5.2. The Committee **recommended** that the Special Authority criteria for febuxostat be amended as follows (deletions in strikethrough, additions in bold), and that the HML criteria be amended in the same way, with a medium priority:

Special Authority for Subsidy

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

Both:

- 1 Patient has been diagnosed with gout; and
- 2 Any of the following:
  - 2.1 The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses of at least 600 mg/day ~~and addition of probenecid at doses of up to 2 g per day or maximum tolerated dose;~~ 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 use of probenecid at doses of up to 2 g per day or maximum tolerated dose;~~ or
  - 2.3 The patient has renal impairment ~~such that probenecid is contraindicated or likely to be ineffective~~ and serum urate remains greater than 0.36 mmol/l despite optimal treatment with allopurinol (see Note).

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

Note: ~~In chronic renal insufficiency, particularly when the glomerular filtration rate is 30 ml/minute or less, probenecid may not be effective.~~ The efficacy and safety of febuxostat have not been fully evaluated in patients with severe renal impairment (creatinine clearance less than 30 ml/minute). No dosage adjustment of febuxostat is necessary in patients with mild or moderate renal impairment. Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/l, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.

- 5.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of 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

- 5.4. The Committee noted that funding of benzbromarone and febuxostat has significantly increased the number of available gout treatments; however, the management of gout remains a significant challenge in New Zealand.

- 5.5. The Committee noted that febuxostat (Adenuric) is currently funded for patients with treatment-resistant gout subject to Special Authority criteria and hospital restrictions. The Committee noted that PHARMAC had recently amended the access criteria for febuxostat, in line with the Committee's February 2015 recommendations, with the exception of the recommended change to the maximum allopurinol dose which was not proposed pending PTAC's re-review of this point.
- 5.6. The Committee noted that the supplier of febuxostat, Te Arai BioFarma, had requested a number of changes to the access criteria, discussed individually below. The Committee also reviewed a response from the New Zealand Rheumatology Association to Te Arai BioFarma on some of the issues raised by the supplier.

***Request to reduce the target urate level from 0.36 mmol/L to 0.30 mmol/L***

- 5.7. The Committee noted that Australian and New Zealand recommendations for the diagnosis and management of gout have recently been published (Graf et al. Int J Rheum Dis. 2015;18:341-51), and that the panel recommended a target serum uric acid of < 0.30 mmol/L when tophi are present based on expert opinion, otherwise < 0.36 mmol/L is sufficient. The Committee noted and agreed with the view of the Rheumatology Subcommittee that that the target serum urate level of 0.36 mmol/L specified in the Special Authority criteria for benzbromarone and febuxostat was reasonable and economically appropriate as a funding requirement, noting that there was nothing in the criteria that would prevent clinicians from attempting to achieve a lower serum urate level with allopurinol and/or probenecid if clinically appropriate prior to using febuxostat or benzbromarone. The Committee considered that there was no compelling reason to amend the serum urate target in the febuxostat funding criteria.

***Request to remove the requirement for probenecid to be trialled prior to febuxostat***

- 5.8. The Committee noted a 1974 study provided by the supplier which was designed to evaluate the usefulness of prophylactic colchicine when used together with probenecid in preventing acute attacks of gout (Paulus et al. Arthritis Rheum. 1974;17:609-14). Fifty two patients were randomised to receive probenecid 500 mg tid and either colchicine 0.5 mg tid or matching placebo; 38 patients were included in the analysis. There were more gout attacks per month in patients taking probenecid alone compared with probenecid plus colchicine (0.48 versus 0.19). There was reduction in serum urate in both groups. Patients taking colchicine had more side effects. The authors concluded that addition of colchicine to probenecid would reduce the frequency of acute attacks of gout in patients whose hyperuricaemia has been controlled by probenecid. The Committee noted the supplier's comment that in this study there was no reduction of acute gout attacks with probenecid in spite of reduction in uric acid (3.2 attacks per year pre-treatment versus 6 per post-treatment). The Committee noted that although the study was a randomised controlled trial, it was quite small and its applicability to the New Zealand population with problems with urate excretion is not clear.
- 5.9. The Committee noted that probenecid is often problematic to use as it is difficult to titrate which sometimes requires additional clinic visits. For this reason the Committee considered that it would be reasonable to remove the requirement for probenecid to be trialled before febuxostat. The Committee noted that the cost of febuxostat was higher than probenecid and considered that the maximum cost of removing the probenecid requirement would be approximately equal to the cost of the current probenecid population switching to febuxostat. The Committee considered it unlikely that febuxostat would completely replace the use of probenecid for gout as probenecid was still viewed as a useful agent. The Committee noted that some of the use of probenecid may be short-term use to achieve higher penicillin concentration
- 5.10. The Committee noted that removal of the requirement to try probenecid prior to accessing funded febuxostat would not prevent clinicians from continuing to prescribe it prior to febuxostat if they considered it clinically appropriate, noting that one potential

advantage of probenecid is that it has a different mechanism of action to allopurinol and febuxostat.

***Request to limit the maximum prerequisite dose of allopurinol to “at least 600 mg/day”***

- 5.11. The Committee noted a number of publications investigating allopurinol dosing, including:
- Stamp et al. *Arthritis Rheum.* 2011;63:412-21.
  - Becker et al. *Semin Arthritis Rheum.* 2015;May 21. doi: 10.1016/j.semarthrit.2015.05.005. [Epub ahead of print]
  - Graham et al. *Br J Clin Pharmacol.* 2013;76:932-8.
- 5.12. Collectively, the Committee considered that the studies supported the use of higher doses of allopurinol to reduce serum urate and that there is no compelling reason not to use doses higher than 600 mg/day, although this may not be achievable in some patients.
- 5.13. The Committee reiterated its previous view that it would be reasonable to increase the maximum required dose of allopurinol to 700-900 mg/day in the benzbromarone and febuxostat funding criteria, noting that the Medafe datasheet for allopurinol recommends doses of 700-900 mg/day in severe conditions.

***Request to permit use of febuxostat as a first-line treatment option in patients who have a baseline serum urate of greater than 0.55 mmol/l***

- 5.14. The Committee noted the results of the FORTE study, a multi-centre, open-label, prospective cohort study conducted to evaluate the use, effectiveness and safety of febuxostat in routine clinical practice (Tausche et al. *Int J Rheumatol.* 2014; doi: 10.1155/2014/123105. Epub 2014 Sep 3). Safety and efficacy data were assessed at baseline and week 4. Data from 5,592 gout patients (72.6% male, mean age 63.7 years) were collected. A total of 80.31% received urate-lowering therapy, of which 78.70% received allopurinol, 0.06% febuxostat, 0.05% probenecid and 1.5% benzbromarone. The main reason for the treating physician to initiate treatment with febuxostat was insufficient efficacy of the previous urate lowering therapy (75.1%). In addition, compliance issues with previous treatment (26.4%) and interactions with concomitant medications (10.5%) were documented. The majority received 80 mg/day of febuxostat (87%) and some received 120 mg/day. Patients also received nutritional and weight reduction counseling. With febuxostat mean serum urate levels decreased significantly from 0.534 mmol/L at baseline to 0.372 mmol/L at week 4. Sixty-seven percent of febuxostat-treated patients reached the mean uric acid target of 0.366 mmol/L. A total of 43.1% of febuxostat patients received concomitant flare prophylaxis.
- 5.15. The Committee considered that the study provides reasonably strong evidence both doses of febuxostat are useful in the treatment of gout; however, the Committee considered that it was insufficient to support an application to fund febuxostat as a first-line option for all patients with a baseline serum urate of greater than 0.55 mmol/l. The Committee noted that the study was sponsored by the industry as a precursor to new urate lowering treatment; patients who showed a lack of response to allopurinol after at least 8 weeks, or who were intolerant to allopurinol, were eligible for participation in phase 3 studies of lesinurad; this may have influenced discontinuation rates, non-escalation of dose, limiting assessments of efficacy and safety.

## **6. Insulin Pumps for Pregnancy**

### **Application**

- 6.1. The Committee considered further evidence for the funding of insulin pumps periconception for women with Type 1 Diabetes following their recommendation from a

paper presented at the November 2014 PTAC meeting for an updated Cost Utility Analysis (CUA).

## Recommendation

- 6.2. The Committee **recommended** that insulin pumps peri-conception for women with Type 1 Diabetes be funded with a low priority. The Committee noted that its priority could increase if the price of insulin pumps were significantly reduced to improve their cost-effectiveness.
- 6.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (vii) The direct cost to health service users; (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

## Discussion

- 6.4. The Committee noted that it had previously reviewed an application for funding insulin pumps in pregnancy at its November 2014 meeting. The Committee also noted its recommendation at that meeting:
- 6.5. The Committee **recommended** that a Cost Utility Analysis (CUA) be undertaken to determine the cost versus health benefits of funding insulin pumps for peri-conception women with Type 1 Diabetes. Members considered that it would be important for the analysis to include the effects of poor glycaemic control on the unborn baby.
- 6.6. The Committee noted that the paper by Bell et al. (*Diabetologia* 2012;55:936-47) presented at the PTAC November 2014 meeting was used to inform the rates of congenital birth anomalies used in the economic analysis. Members considered that in this study HbA1c >7% (53 mmol/mol) was associated with an increased risk of congenital anomalies.
- 6.7. The Committee reviewed an updated cost-effective analysis of insulin pumps peri-conception for women with Type 1 Diabetes. The Committee noted that the patient group modelled was those with an HbA1c between 53 - 65 mmol/mol and agreed that this was the appropriate patient group that would be eligible for funding. This group does not have access to funding under the current special authority criteria. The Committee considered that there would be approximately 70 women per year in this patient population. The Committee noted that some of these women, over time, would become eligible for insulin pumps through the current criteria.
- 6.8. The Committee noted it would be difficult to establish a special authority that included stopping criteria for this patient group. The Committee agreed that overall, the assumptions used in the economic model were appropriate. Members considered the endpoints of mortality and congenital anomaly for the unborn baby were appropriate, including the use of VSD, spina bifida, renal disease and talipes equinovarus. The Committee considered that the costs associated with congenital anomaly that were used in the economic model may have been too low. However, Members were satisfied that this was accounted for in the sensitivity analysis.
- 6.9. The Committee considered that the benefits of a reduction of HbA1c below 53 mmol/mol, in terms of congenital anomalies, are not apparent in the Bell paper. Members noted that this view aligns with that of the American Diabetes Association.
- 6.10. The Committee considered that the result of the updated analysis indicate that, due to the high cost of insulin pumps and the relatively small benefit with regards to mortality

and congenital anomalies on the unborn baby, the cost effectiveness of insulin pumps peri-conception for women with Type 1 Diabetes with an HbA1c ranging between 53 - 65 mmol/mol was poor.

## 7. Bendamustine for Chronic Lymphocytic Leukaemia Non Hodgkin's Lymphoma

### Application

- 7.1. The Committee reviewed an application, first received in July 2013, for funding of bendamustine (Ribomustine, Janssen) for the treatment of treatment naive or relapsed refractory follicular and mantle cell lymphoma from Lymphoma New Zealand (a special interest group with representation from NZ specialist haematologists, oncologists, radiation oncologists).
- 7.2. The Committee also reviewed a subsequent application for bendamustine from its supplier, Janssen, received in August 2014, for:
- monotherapy for the first-line treatment of CLL for patients unable to tolerate treatment with FCR (fludarabine, cyclophosphamide and rituximab); and
  - In combination with rituximab for the first-line treatment of patients with indolent NHL, including MCL; and
  - for the treatment of patients with relapsed or refractory indolent NHL with or without rituximab.
- 7.3. Members noted that the funding application from the supplier was for a wider population than the clinician funding application.

### Recommendation

- 7.4. The Committee **recommended** that bendamustine be funded with medium priority for the first-line treatment of patients with Chronic Lymphocytic Leukaemia unable to tolerate treatment with FCR.
- 7.5. The Committee **recommended** that bendamustine be funded with low priority for first-line treatment of patient with indolent Non-Hodgkin's Lymphoma.
- 7.6. The Committee deferred making a recommendation for the funding of bendamustine for the treatment of patients with relapsed or refractory indolent Non-Hodgkin's Lymphoma pending publication of study NHL 2-2003.
- 7.7. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for advice regarding the place in therapy of bendamustine and inputs for the cost effectiveness model including the likely age that patients commence treatment and utility values. Members were particularly interested in a view on the relative place in therapy of bendamustine and obinutuzumab.
- 7.8. 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

- 7.9. The Committee noted that CLL is an indolent disease with variable clinical course. Members noted that most patients did not require treatment at initial diagnosis and are monitored using a watch-and-wait strategy, with treatment initiation generally delayed until the disease became active or symptomatic. Members noted that currently in New

Zealand fit patients requiring first-line systemic treatment received rituximab in combination with fludarabine and cyclophosphamide (FC-R) whilst older patients who were less fit with comorbidities receive chlorambucil monotherapy.

- 7.10. The Committee noted that the key evidence for the use of bendamustine in CLL was a randomised, open-label, Phase III study of bendamustine compared with chlorambucil in previously untreated patients with advanced (Binet stage B or C) CLL (Knauf et al. J Clin Oncol. 2009; 27: 4378-84 and Knauf et al., Br J Haematol. 2012; 159: 67-77). Members noted that 319 patients up to 75 years old were randomised 1:1 to receive bendamustine (n=162) 100 mg/m<sup>2</sup>/d administered intravenously over 30 minutes on days 1 to 2, or chlorambucil (n=157) 0.8 mg/kg orally on days 1 and 15 with treatment cycles repeated every 4 weeks for a maximum of six cycles.
- 7.11. The Committee noted that the primary end points of the study were overall response rate and progression-free survival (PFS). Secondary end points included time to progression, duration of remission, and overall survival (OS) and safety.
- 7.12. The Committee noted that median PFS was improved by 12.4 months in the bendamustine treated group (median PFS 21.2 months) compared with chlorambucil (median PFS 8.8 months, p< 0.0001; hazard ratio 2.83). Members noted that overall response rate was higher for bendamustine with 110 bendamustine-treated patients (68%), and 48 (31%) chlorambucil-treated patients achieving a complete or partial response (CR or PR, P<.0001). Members noted that median OS had not yet been reached in the bendamustine group and was 78.8 months for the chlorambucil group. Members noted that although the hazard ratio for death favoured bendamustine, second line bendamustine treatment was used in approximately one quarter of the chlorambucil treated patients which confounded interpretation of the survival data. Members noted that a total of 103 (63.6%) patients in the bendamustine group and 123 (78.3%) of those in the chlorambucil group subsequently received second-line or further lines of treatment (p = 0.004).
- 7.13. The Committee noted that haematologic adverse events were more frequent in the bendamustine arm (neutropenia in 27%, thrombocytopenia in 25%, and anaemia in 22% of patients) than in the chlorambucil arm (neutropenia in 14%, thrombocytopenia in 21%, and anaemia in 14% of patients) and gastrointestinal events (nausea, vomiting, and diarrhoea) were also more frequent with bendamustine. Members noted that 36% of patients in the bendamustine group compared with 4% in the chlorambucil group received antiemetics.
- 7.14. The Committee considered that the Knauf study was of good quality but considered that the patients enrolled in study were relatively young with an average age of 63, compared to the average age of diagnosis of CLL in New Zealand which was around 72 years. Overall members considered that although a 12 month PFS gain for bendamustine was reported that because CLL was generally an indolent disease the proportionate gain was not large. Members considered that OS data would be more useful and that this outcome was not as robust because OS data was confounded by cross-over treatment.
- 7.15. Members considered that if bendamustine was funded approximately two-thirds of patients would receive chlorambucil as a second line treatment. Members also considered that the supplier's estimates of number of patients that would be treated was conservative. The Committee considered it more likely that around 35 patients would be treated (approximately one-sixth of 215 newly diagnosed CLL/SLL cases Ministry of Health Cancer: New Registrations and Deaths 2011). Members also noted that additional patients with marginal fitness currently being treated with dose-modified FCR may instead be treated with bendamustine if it were funded.

- 7.16. The Committee noted that several other new treatments are in development or have recently been registered for the treatment of CLL including: ofatumumab, obinutuzumab, ibrutinib and idelalisib. Members noted that it had recently recommended that obinutuzumab be funded with medium priority for the same population as being proposed for bendamustine and therefore it was a direct competitor. Members noted that ofatumumab was used in combination with chlorambucil and may be combined with bendamustine. Ibrutinib and idelalisib are positioned as second line treatments.

### **Indolent Non-Hodgkin's Lymphoma (iNHL)**

- 7.17. The Committee noted that the grade and stage of NHL informs prognosis and treatment choice. Members noted that current chemotherapy regimens routinely used for symptomatic- low grade NHL in New Zealand include 6-8 cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone).
- 7.18. The Committee noted key evidence was a randomised, open-label, non-inferiority phase III trial comparing treatment with bendamustine plus rituximab (BR n=274) or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP n=275) for a maximum of 6 cycles in treatment naïve patients with indolent or mantle-cell lymphomas (NHL1-2003 (StiL study): Rummel et al. *Lancet*. 2013; 381: 1203-10). Members noted that the primary endpoint of the study was progression-free survival with secondary endpoints including rates of overall and complete response; toxicity; overall survival; time to next anti-lymphoma treatment; and event-free survival.
- 7.19. The Committee noted that progression-free survival was 38 months (> 3 years) longer in the BR group compared with the R-CHOP group (BR median PFS 69.5 months [vs R-CHOP median PFS 31.2 months; HR 0.58, 95% CI 0.44–0.74; p<0.0001). Members noted that this benefit was evident across all histological subtypes, except for marginal-zone lymphoma.
- 7.20. The Committee noted that the publication reported that "Overall survival did not differ between the treatment groups (appendix); 43 patients died in the bendamustine plus rituximab group compared with 45 in the R-CHOP group. Median overall survival was not reached in either group (appendix)". However, members noted that there was no OS data provided in the appendix and there was no information provided in the publication regarding cross-over between treatment arms.
- 7.21. The Committee also noted evidence from an open label, RCT of bendamustine plus rituximab vs R-CHOP/R-CVP in for treatment naïve patients with indolent non-Hodgkin's lymphoma or mantle cell lymphoma (the BRIGHT study Flinn et al. *Blood* 2014; 123: 2944-52) but considered it less useful than the StiL study as its primary endpoint was complete response rate. Members noted that whilst PFS and OS were cited as secondary endpoints in the study neither were reported in the publication.
- 7.22. The Committee considered that the trial evidence supports is bendamustine superior to CHOP for PFS but considered the evidence in relation to OS, a more important outcome for this disease, was poor.
- 7.23. The Committee considered that, if funded, bendamustine would defer the use of R-CHOP/CVP to a later line of treatment in approximately half of patients. The Committee considered that the supplier's uptake estimates were conservative. The Committee considered that up to 75% of eligible patients, approximately 225 annually, would be treated if bendamustine was funded (with reference to the Ministry of Health Cancer: New Registrations and Deaths 2011, which recorded 133 Follicular Lymphoma, and 172 other mature B-cell NHL cases).

### **Relapsed refractory Non-Hodgkin's Lymphoma (RRNHL)**

- 7.24. The Committee considered that for relapsed/refractory NHL key evidence was a randomised controlled study comparing bendamustine plus rituximab (BR) versus fludarabine rituximab (FR) in patients with relapsed follicular, indolent or mantle cell lymphoma, study NHL 2-2003. However, members noted that whilst the study had been presented by Rummel et al. at American Society of Haematology meeting in 2010 it remained unpublished in a peer-reviewed journal.
- 7.25. The Committee considered that the abstract of the unpublished Rummel et al. study looked encouraging but considered that full publication was required before conclusions could be drawn. The Committee considered that the supplier's uptake estimates were too conservative; members considered that approximately 60 patients annually would be treated if bendamustine was funded in this setting.
- 7.26. Members noted evidence from five non-randomised studies of bendamustine in this setting had been published; however, considered that the strength and quality of this evidence was weak.

## 8. Pemetrexed for advanced non-squamous non-small cell lung carcinoma

### Application

- 8.1. The Committee considered an application from a clinician for the funding of pemetrexed as for first-line, maintenance, and second-line treatment of patients with advanced non-squamous non-small cell lung cancer.

### Recommendation

- 8.2. The Committee **recommended** that pemetrexed be funded only if cost neutral for the first-line treatment of patients with advanced non-squamous non-small cell lung carcinoma.
- 8.3. The Committee **recommended** that pemetrexed be funded with a low priority for maintenance treatment of patients with advanced non-squamous non-small cell lung carcinoma.
- 8.4. The Committee **recommended** that pemetrexed be funded only if cost neutral for second-line treatment of patients with advanced non-squamous non-small cell lung carcinoma in patients who had not received prior treatment with pemetrexed.
- 8.5. The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

- 8.6. The Committee noted that PTAC had previously considered applications from Eli Lilly, the supplier of pemetrexed, for the funding of pemetrexed for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum-based chemotherapy (i.e. second-line therapy) and as a first-line for patients with locally advanced or metastatic non-squamous NSCLC.
- 8.7. The Committee noted that much of the evidence presented in the application had previously been considered by the Committee at meetings in 2006, 2007 and 2008 but that new evidence had also been provided. Members noted new evidence included publications of pemetrexed studies in first-line (Scagliotti et al. (J Clin Oncol 2008; 26:3543-51), and maintenance treatment (Ciuleanu et al (Lancet 2009 ;374(9699):1432-40 and Paz-Ares et al. Clin Lung Cancer 2014;15:418-25).

- 8.8. The Committee noted that over a million people worldwide die every year from lung cancer and more than 87% of the cases are NSCLC. Members also noted that approximately 40% of patients have either stage IIIB disease with malignant effusion or stage IV disease at presentation.
- 8.9. The Committee considered the relevant evidence for each setting being requested for funding.

### First-line

- 8.10. The Committee considered that platinum based doublet chemotherapy is the current standard first-line treatment for patients with advanced NSCLC in New Zealand. Members noted that in New Zealand there was a preference for platinum plus paclitaxel to be used rather than platinum plus gemcitabine as it was easier to administer. Members considered that outcomes for cisplatin/carboplatin plus paclitaxel would be similar to cisplatin plus gemcitabine and that this was an appropriate comparator for pemetrexed. The Committee considered that less than 40% of patients would be expected to respond to cisplatin plus gemcitabine and that response usually occurred after 2-4 cycles of treatment. Members noted that toxicity usually prevents more than 4 cycles of treatment and few of the patients who fail to respond to first-line treatment are fit enough to receive second-line treatment.
- 8.11. The Committee noted evidence from a randomised, phase III, -non-inferiority trial (Scagliotti et al. J Clin Oncol 2008;26:3543-51) in 1725 chemotherapy-naive patients with stage IIIB or IV NSCLC with an ECOG performance score of 0 to 1. Members noted that patients received pemetrexed plus cisplatin (CP: pemetrexed 500 mg/m<sup>2</sup> plus cisplatin 75 mg/m<sup>2</sup> day 1 every 21 days) (n=862) or gemcitabine plus cisplatin (CG: gemcitabine 1250 mg/m<sup>2</sup> days 1 and 8 plus cisplatin 75 mg/m<sup>2</sup> days 1 every 21 days) (n=863). Members noted that the primary endpoint of the trial was overall survival (OS) and that treatment was continued until progressive disease, unacceptable toxicity or the investigator decided to discontinue the treatment, or the patient requested discontinuation.
- 8.12. The Committee noted that the primary end point in the trial of non-inferior OS in NSCLC was met with median overall survival time of 10.3 months for both treatment arms (HR=0.94, 95% CI, 0.84 to 1.05). However, members noted that a pre-specified analysis of OS by NSCLC histology suggested a benefit for pemetrexed in non-squamous NSCLC; conversely in squamous NSCLC gemcitabine treatment appeared more beneficial. However, members considered that the benefits, if any, were marginal at best and questioned the statistical methodology.
- 8.13. The Committee noted that pemetrexed treatment was associated with fewer adverse events. The Committee noted that the incidence of grade 3/4 haematological toxicities were significantly lower for pemetrexed compared with gemcitabine (neutropenia 15% vs. 27%; anemia, 6% vs. 10%, thrombocytopenia 4% vs. 13%, and febrile neutropenia 1% v 4%) and the incidence of alopecia was also significantly lower (12% vs 21%). Members further noted that patients treated with pemetrexed received significantly fewer transfusions 16.4% vs. 28.9%, including red blood cell transfusions (16.1 % vs. 27.3%) and platelet transfusions (1.8% vs. 4.5%) and fewer administrations of erythropoietin (10.4% vs. 18.1%) and granulocyte colony-stimulating factors (3.1 % vs. 6.1 %). Members noted that whilst febrile neutropenia in this setting was serious, its costs were lower than in haematological settings. The Committee suggested PHARMAC assume a 2-day stay in hospital for this adverse event for CUA purposes.
- 8.14. The Committee considered that in the first-line NSCLC setting there was good evidence that pemetrexed was non-inferior to gemcitabine and it was better tolerated. Members considered that there was moderate evidence that pemetrexed was more beneficial than current treatments in non-squamous NSCLC but members considered that the survival gains in this setting were marginal. Members considered that the gains for pemetrexed

were not sufficient to justify its current cost; however, members noted that generic versions of pemetrexed were now available which should reduce its cost. Members considered that pemetrexed should be funded in this setting if its pricing was cost neutral to gemcitabine taking into account the cost of treating gemcitabine related haematological adverse events.

## Maintenance

- 8.15. The Committee noted evidence from a randomised phase III double blind study in 663 patients with stage IIIB or IV NSCLC who had not progressed on four cycles of first-line platinum-based chemotherapy (Ciuleanu et al. *Lancet* 2009;374 :1432-40). Patients were randomised 2:1 (2:1 ratio) to receive maintenance treatment with pemetrexed (500 mg/m<sup>2</sup>, day 1) plus best supportive care (n=441) or placebo plus best supportive care (n=222) in 21-day cycles until disease progression. The Committee noted that pemetrexed significantly improved progression-free survival, the primary endpoint of the study, (4.3 months [95% CI 4.1-4.7] vs 2.6 months [1.7-2.8]; hazard ratio [HR] 0.50, 95% CI 0.42-0.61, p<0.0001) and overall survival (13.4 months [11.9-15.9] vs 10.6 months [8.7-12.0]; HR 0.79, 0.65-0.95, p=0.012) compared with placebo. The Committee noted that treatment discontinuations due to drug-related toxic effects were higher in the pemetrexed group than in the placebo group 5% vs. 1%. Members also noted that drug-related grade three or higher toxic effects were higher with pemetrexed than with placebo (70 [16%] vs nine [4%]; p<0.0001), specifically fatigue (22 [5%] vs one [1%], p=0.001) and neutropenia (13 [3%] vs 0, p=0.006).
- 8.16. The Committee also noted evidence from the phase 3, randomised double-blind, placebo-controlled study in patients with advanced non-squamous NSCLC, also known as the PARAMOUNT study (Paz-Ares et al. *Lancet Oncol* 2012;13:247-55 and Paz-Ares et al. *J Clin Oncol* 2013; 31:2895-902). Members noted that before randomisation, patients entered an induction (first-line treatment) phase which consisted of four cycles of pemetrexed (500 mg/m<sup>2</sup>) plus cisplatin (75 mg/m<sup>2</sup>) on day 1 of a 21-day cycle. Following induction, 539 patients whose disease had not progressed during the induction phase were randomly assigned 2:1 to receive maintenance therapy with either pemetrexed (500 mg/m<sup>2</sup> every 21 days) plus best supportive care (n=359) or placebo plus best supportive care (n=180) until disease progression. The Committee noted a similar gain in median progression free survival to the previous study of 4.1 months (95% CI 3.2-4.6) for pemetrexed vs 2.8 months (2.6-3.1) for placebo.
- 8.17. The Committee also noted final overall survival analysis from this study demonstrating that pemetrexed treatment statistically significantly reduced the risk of death (HR, 0.78; 95% CI, 0.64 to 0.96; P=.0195); with median OS of 13.9 months for pemetrexed compared with 11.0 months for placebo. The mean number of cycles of maintenance treatment administered was 7.9 for pemetrexed and 5.0 for placebo. Members noted that the proportion of patients receiving additional therapy post discontinuation of pemetrexed was similar in both arms: 64% (n=231) for pemetrexed and 72% (n=129) for placebo

## Second Line

- 8.18. The Committee considered evidence from a randomized phase III trial of pemetrexed versus docetaxel in patients with NSCLC previously treated with chemotherapy (Hanna et al. *J Clin Oncol* 2004;22:1589-97). Members noted that PTAC had previously considered this evidence. Members noted that pemetrexed was non-inferior to docetaxel but appeared to have a better toxicity profile. Members noted in particular the higher incidence of grade 3/4 neutropenia and febrile neutropenia (FN) with docetaxel but noted that in this setting the duration of neutropenia/FN was relatively short and the costs of the was very low compared with the high additional cost of pemetrexed. Members considered that patients would be hospitalised for a maximum of 2-3 days and would receive intravenous antibiotics and GSCF treatment.

- 8.19. The Committee noted new evidence (Scagliotti et al. J Thorac Oncol 2011;6:64–70) from a post hoc pooled analysis combining data from the three registration studies for pemetrexed [second line (N=571) (Hanna et al. 2004, as above), first-line (N=1725) (Scagliotti et al. J Clin Oncol 2008;26:3543-51), and one of the maintenance studies (N=663) (Ciuleanu et al. Lancet 2009;374:1432–40)] examining the interaction between treatment effect and NSCLC histology. Members noted that the study reported a statistically significant interaction between treatment effect and NSCLC histology, indicating superior efficacy of pemetrexed in non-squamous histology NSCLC patients compared with other standard treatment options, however, members considered that this benefit was quite marginal.
- 8.20. Overall the Committee considered that pemetrexed was a reasonable alternative to other currently funded treatment options but its current cost was too high relative to its benefits. Members noted that generic pemetrexed was now available and considered that at cost neutral pricing, including the costs of treating adverse events in particular neutropenia/FN, it would be supportive of funding pemetrexed.

## 9. **Bevacizumab (Avastin) for the first-line treatment of recurrent, persistent or metastatic cervical cancer**

### Application

- 9.1. The Committee considered a clinician application submitted on behalf of the NZ Gynaecological Cancer Group (NZGCG) for the funding of bevacizumab in combination with chemotherapy for recurrent, persistent or metastatic cervical cancer.

### Recommendation

- 9.2. The Committee **recommended** that bevacizumab with chemotherapy should be funded for patients with recurrent, persistent or metastatic cervical cancer with a low priority. The Committee considered that if listed, its use should be restricted to specialist oncologists for the indication of advanced or metastatic cervical cancer.
- 9.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

### Discussion

- 9.4. The Committee noted that in 2011 there were 165 registrations and 53 deaths from cervical cancer in New Zealand, and it accounted for 1.7% of all female cancer registrations and 1.2% of all female deaths from cancer. The Committee noted that cervical cancer disproportionately affects Māori women with incidence rates twice that of non-Māori women and mortality rates 3.9 times higher than non-Māori women however it did not consider that listing bevacizumab would significantly reduce health disparities between the groups given the already advanced progression of the disease. The Committee considered that rather than investing in new treatments, increasing the uptake of cervical screening and HPV immunisation would be a more efficient way to reduce this inequity.
- 9.5. The Committee noted that metastatic disease will develop in 15 to 61 percent of women with cervical cancer, usually within the first two years of initiating treatment. Members noted that initial treatment for localised cervical cancer usually comprised surgery with or without radiotherapy. For patients with local recurrence, surgery and radiation can also be combined with chemotherapy. Members noted that patients with metastatic disease may have palliative surgery but are usually treated with chemotherapy.

- 9.6. The Committee noted that the current standard chemotherapy treatment given in New Zealand is platinum (carboplatin or cisplatin) in combination with paclitaxel.
- 9.7. The Committee noted that bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A), originally developed for the treatment of metastatic colon cancer and has since received approvals for the treatment of advanced/metastatic lung, renal, ovarian, cervical, and breast cancers and glioblastoma multiforme of the brain. The Committee noted that bevacizumab in New Zealand is currently funded in DHB hospitals for the treatment of ocular neovascularisation and exudative ocular angiopathy, both of which are off label indications.
- 9.8. The Committee noted that the key clinical evidence supporting the use of bevacizumab in cervical cancer from a randomised controlled phase III 4-arm study comparing 2 different chemotherapy regimens with, and without, bevacizumab, GOG 240 (Tewari KS et al. N Engl J Med. 2014;370:734). The Committee noted that the Tewari 2014 study enrolled 425 patients with metastatic, persistent, or recurrent cervical carcinoma who were randomised to one of 4 treatment arms: cisplatin (50 mg/m<sup>2</sup>) plus paclitaxel (135 or 175 mg/m<sup>2</sup>), on day 1 with or without bevacizumab (15 mg/kg on day 1) or topotecan (0.75 mg/m<sup>2</sup> on days 1 to 3) plus paclitaxel (175 mg/m<sup>2</sup> on day 1) with or without bevacizumab. Treatment cycles were repeated every 21 days until disease progression or the development of unacceptable toxic effects, or if the patient had a complete response. Members noted that the majority of patients enrolled in the study had recurrent disease, and more than 70% of patients had previously received platinum-based chemoradiotherapy.
- 9.9. The Committee considered the Tewari et al., NEJM 2014 trial to be representative of the New Zealand population with advanced or metastatic cervical cancer who are currently treated with chemotherapy. Members noted that cisplatin and paclitaxel are currently standard treatment in New Zealand.
- 9.10. Members noted that topotecan was not currently available in New Zealand. Members noted that Tewari et al. considered the topotecan plus paclitaxel regimen to be neither superior nor inferior to the cisplatin plus paclitaxel regimen. The Committee considered this to be a fair assumption.
- 9.11. The Committee noted that bevacizumab significantly improved the median progression free survival (PFS) and overall survival (OS) compared with chemotherapy alone with gains of 2.3 months in PFS (8.2 vs. 5.9 months; hazard ratio for disease progression, 0.67; 95% CI, 0.54 to 0.82) and 3.7 months in OS (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% CI, 0.54 to 0.95). Members also noted the response rate was significantly higher among patients who received bevacizumab (48% vs. 36%) with relative probability of a response, 1.35; 95% CI, 1.08 to 1.68; P = 0.008. Members noted that 28 of the patients who received bevacizumab had a complete response, compared with 14 who received chemotherapy alone; members noted that treatment was discontinued in 21 patients who had a complete response but noted that it was not clear in the study what the long term outcomes for these patients were.
- 9.12. The Committee considered the evidence to be moderately strong and of good quality although members noted that the study had a factorial design but that the study report only reported main effects and not interactions between treatments..
- 9.13. The Committee noted that although there were gains in PFS and OS with bevacizumab, treatment with bevacizumab was also associated with an increased incidence of adverse events, most notably hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%). The Committee considered that these side effects may

cause significant health losses and costs, and therefore needs to be balanced with the potential benefit of treatment.

- 9.14. The Committee noted the high cost of bevacizumab and the results of two cost-utility studies conducted in the US setting (Phippen et al., *Gynecologic Oncology*, 2015;136:43-7 and Minion et al., *Gynecologic Oncology* 2015; 137:490-6) which reported cost effectiveness of US\$155,000 and US\$295,000 per QALY gained respectively. The Committee noted that these results were similar to that estimated by PHARMAC staff. The Committee considered that the cost of bevacizumab was disproportionate to its benefits.

## 10. Tocilizumab (Actemra) for polyarticular juvenile idiopathic arthritis

### Application

- 10.1. The Committee considered an application from Roche Products (New Zealand) Limited to fund intravenous tocilizumab (Actemra) for the treatment of polyarticular juvenile idiopathic arthritis in patients experiencing tumour necrosis factor alpha inhibitor failure or contraindication.

### Recommendation

- 10.2. The Committee **recommended** that intravenous tocilizumab (Actemra) be listed in Part II of Section H of the Pharmaceutical Schedule subject to the following hospital medicines list (HML) restrictions, with a medium priority:

#### Initiation – polyarticular juvenile idiopathic arthritis

Rheumatologist

*Re-assessment required after 4 months.*

Either:

1 Both:

- 1.1 The patient has had an initial Special Authority approval for both etanercept and adalimumab for juvenile idiopathic arthritis (JIA); and
- 1.2 The patient has experienced intolerable side effects, or has received insufficient benefit from, both etanercept and adalimumab; or

2 All of the following:

- 2.1 Treatment with a tumour necrosis factor alpha inhibitor is contraindicated; and
- 2.2 Patient has had severe active polyarticular course JIA for 6 months duration or longer; and
- 2.3 Patient has tried and not responded to at least three months of oral or parenteral methotrexate (at a dose of 10-20 mg/m<sup>2</sup> weekly or at the maximum tolerated dose) in combination with either oral corticosteroids (prednisone 0.25 mg/kg or at the maximum tolerated dose) or a full trial of serial intra-articular corticosteroid injections; and
- 2.4 To be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and

2.5 Both:

2.5.1 Either:

- 2.5.1.1 Patient has persistent symptoms of poorly-controlled and active disease in at least 20 swollen, tender joints; or
- 2.5.1.2 Patient has persistent symptoms of poorly-controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, shoulder, cervical spine, hip; and

2.5.2 Physician's global assessment indicating severe disease.

**Renewal** – polyarticular juvenile idiopathic arthritis

Rheumatologist

*Re-assessment required after 6 months*

Both:

1 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and

2 Either:

2.1 Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count and an improvement in physician's global assessment from baseline; or

2.2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count and continued improvement in physician's global assessment from baseline.

- 10.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

**Discussion**

- 10.4. The Committee noted that polyarticular juvenile idiopathic arthritis (pJIA) is one of seven types of JIA, and typically affects five or more joints during the first six months of illness and can begin at any age.

- 10.5. The Committee noted that there are a number of funded treatments available for use in pJIA, including non-steroidal anti-inflammatory agents (NSAIDs), methotrexate, oral corticosteroids and intra-articular corticosteroids. The Committee noted that the tumour necrosis factor (TNF) alpha inhibitors adalimumab and etanercept are currently funded as last-line treatments for pJIA subject to Special Authority criteria and hospital medicines list (HML) restrictions.

- 10.6. The Committee noted that there are currently approximately 113 patients with pJIA with Special Authority approvals for adalimumab (n=31) or etanercept (n=82). The Committee noted that since adalimumab became funded for pJIA on 1 July 2013, 22 patients have switched from etanercept to adalimumab (17 of whom switched due to etanercept inefficacy and 5 due to etanercept side effects) and 29 have switched from adalimumab to etanercept (25 due to adalimumab inefficacy and 4 due to adalimumab side effects).

- 10.7. The Committee considered that there is no particular problem with access to or availability of current funded treatments. However, the Committee noted that up to a third of patients with pJIA receive inadequate response to non-biologic disease-modifying antirheumatic agents (DMARD)s and agreed with the view of the Rheumatology Subcommittee that there is an unmet clinical need in patients with pJIA who have received insufficient benefit from TNF inhibitors. The Committee noted that this group of patients generally has severe disease and is associated with greater hospital admissions, physiotherapy and less ability to perform daily activities (eg going to school). The Committee considered that, given the level of disability, this group of patients would be motivated to receive further treatment.

- 10.8. The Committee noted that it had previously reviewed an application to fund rituximab for pJIA, and recommended that the application be declined. The Committee considered that the evidence for rituximab in pJIA was weak and of poor quality, and noted that pJIA is not a registered indication for rituximab. The Committee had significant concerns about the safety of rituximab in this patient group, particularly with respect to the risk of infections. The Committee considered that it would be more appropriate to review

tocilizumab for this patient group given that this was a registered indication for tocilizumab.

10.9. The Committee noted that the supplier of tocilizumab subsequently submitted a funding application for tocilizumab for this patient group, and an additional group of patients with pJIA who have received insufficient benefit from non-biologic DMARDs and in whom TNF inhibitors are contraindicated.

10.10. The Committee noted that tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass, which binds to human interleukin 6 (IL-6) receptors. The Committee noted that tocilizumab (Actemra) is currently listed on the HML for use in DHB hospitals as a last-line biologic treatment for rheumatoid arthritis; as a first-line biologic treatment for rheumatoid arthritis in patients who cannot take methotrexate; as a first-line biologic treatment for systemic JIA; and as a first- or second-line biologic treatment for adult-onset Still's disease. It is given as an intravenous infusion at a dose of 10mg/kg (patients <30 kg) or 8 mg/kg (patients ≥30 kg) every 4 weeks.

10.11. The Committee noted that the key clinical trial evidence to support the use of tocilizumab for the treatment of pJIA comes from the CHERISH trial (Brunner et al. Ann Rheum Dis 2015;74:1110-7); a phase III, three part, randomised, double-blind withdrawal study to evaluate the efficacy of tocilizumab in patients with active pJIA who have had an inadequate response to methotrexate.

- Eligible patients were 2-17 years old, diagnosed with rheumatoid factor-positive or rheumatoid factor-negative pJIA or extended oligoarticular JIA for ≥ 6 months, five or more active joints (or three or more with limitation of motion), and had an inadequate response to methotrexate or were intolerant of methotrexate. Any previous biologic treatments were discontinued between at least 1 and 20 weeks prior to baseline. A total of 61 patients (32%) had received one or more biologic treatment before commencing the trial, and 9% of patients received three or more biologic agents before commencing the trial. Exclusion criteria included treatment with DMARDs (other than methotrexate) within 4 weeks prior to baseline and previous treatment with tocilizumab. Patients could receive stable doses of NSAIDs, low-dose glucocorticoids and methotrexate.
- Part I of the trial was a 16 week, active treatment, open label, lead in period where 188 patients received tocilizumab every 4 weeks at a dose of 8mg/kg for patients ≥30kg or less (n=119) and 8mg/kg (n=34) or 10mg/kg (n=35) for patients <30kg.
- Part II was a 24 week, double-blind, 1:1 randomisation of 163 patients who had achieved a JIA-ACR30 improvement at week 16 to receive either placebo (n=81) or tocilizumab (n=82) as in part I and stratified by methotrexate and glucocorticoid use. Fifteen patients (7.9%) patients who had an insufficient JIA-ACR response were withdrawn from the study after part I, 3 refused treatment, 1 was lost to follow up, and 3 had severe adverse events such that treatment was discontinued.
- After a JIA-flare (30 or greater worsening in three of the six JIA-CRVs without more than 30% improvement in more than on remaining JIA-CRV) or upon completion of part II patients entered part III of the study; a 64 week, open label, active treatment where patients received tocilizumab at the same dose as in part I. Two patients did not progress to part III as they had an insufficient response, 1 withdrew consent, and 3 had severe adverse events such that treatment was discontinued.
- The primary clinical endpoint was the proportion of patients in whom a JIA-flare occurred during part II (up to and including week 40) compared with week 16.

- At the end of part II (week 40), JIA-flare occurred in 48.1% of patients on placebo vs 25.6% continuing tocilizumab (95% CI -0.35 to -0.08; p= 0.0024). Secondary endpoints of JIA-ACR70 and JIA-ACR90 responses for patient receiving tocilizumab at the end of part II were 64.6% and 45.1% respectively. No differences were observed in response to tocilizumab between patients who were rheumatoid factor-positive and those rheumatoid factor-negative. Adverse events included pneumonia, bronchitis and cellulitis. Infections were the most common serious adverse event (4.9 per 100 patient years).
  - Previous methotrexate and/or steroid use did not seem to affect result. However, previous biologic use was associated with a reduced JIA-ACR70 response (72.7% in patients who had no previous biologic agent versus 48.1% in those who had received one or more previous biologic treatments).
- 10.12. The Committee noted that subgroup analyses showed that a significant number of patients who received tocilizumab in part I and then switched to placebo in part II had a JIA-ACR70 response at the end of part II, for example 55% (32/58) of placebo patients who had not received previous biologic and had a JIA-ACR70 response. The Committee considered that it would have been useful for the total placebo JIA-ACR70 and JIA-ACR90 response rates to have been included in the publication.
- 10.13. The Committee considered that the CHERISH trial provides good quality and strength evidence for the efficacy of tocilizumab in patients with pJIA who have responded poorly to methotrexate. However, the Committee noted that only a third of patients had received a prior biologic treatment, (unlike the patient population under consideration for funding which would have all received a prior biologic) and those patients had a much lower response to tocilizumab.
- 10.14. The Committee considered that other currently available evidence was of poor quality and strength, noting that it consisted mainly of open-label studies and case series/reports (e.g. Imagawa et al., *Modern Rheumatology* 2012;22:109-15; Pontikaki et al., *Ann Rheum Dis* 2011;70(Suppl3):403; Bustabad et al., *Ann Rheum Dis* 2013;72(Suppl 3):1001; Kasai et al, *Int journal of Rheumatic Disease*. 2010;13(Suppl1):200).
- 10.15. The Committee noted that there is a lack of long-term safety data for tocilizumab in children and the long-term effect of IL-6 inhibition in children is unknown. For this reason, the Committee supported the use of tocilizumab after biologic treatments with more well-established safety profiles, ie the TNF alpha inhibitors etanercept and adalimumab.
- 10.16. The Committee considered that, if used at the same point in the disease course as the TNF alpha inhibitors, tocilizumab would likely provide a similar therapeutic effect to the TNF alpha inhibitors, although there was no comparative study to support this. However, the results of the CHERISH study suggest that the efficacy of tocilizumab would be reduced for each line of prior biologic treatment. Despite this, the Committee considered that given the different mechanism of action of tocilizumab it was possible that tocilizumab may benefit some patients who have had an inadequate response to TNF alpha inhibitors.
- 10.17. The Committee considered that for the purposes of PHARMAC's analyses it would be reasonable to assume a lower JIA-ACR50 response rate than reported in the trial for the whole tocilizumab group, as the subgroup analyses suggested that the JIA-ACR response rates in people who had received previous biologic treatment was 20%-30% lower.
- 10.18. The Committee considered that, in the patient group for which funding is sought, tocilizumab would be used as an add-on therapy to methotrexate and would replace the

use of TNF alpha inhibitors in poorly responding patients. The Committee considered that up to a third of current patients on TNF alpha inhibitors could switch to tocilizumab if it was funded for pJIA and it was possible that patients would switch to tocilizumab after their first TNF alpha inhibitor rather than try another TNF alpha inhibitor first. The Committee considered that expenditure on pJIA biologic treatment overall would increase if tocilizumab was funded as requested, as this would prolong the time of patients on biologic treatment.

- 10.19. In terms of dosing assumptions used for PHARMAC's analyses, the Committee noted that 37% of patients in the CHERISH study were under 30 kg (mean weight 39.6 kg) and this would be a reasonable assumption to use. The Committee considered that patients would likely stay on treatment, meaning that their average weight would increase over time.
- 10.20. The Committee noted that infusion costs for children were generally higher than for adults as it is harder to get an infusion line in children (sometimes taking 1-1.5 hours) and there is generally more specialist involvement with children as well. The Committee **recommended** that this be factored into any cost-utility analysis.
- 10.21. The Committee considered that it would be reasonable to require a trial of both etanercept and adalimumab prior to accessing tocilizumab, taking into account the clinical benefits and risks of the treatments and the costs associated with community TNF alpha inhibitors and tocilizumab.

## **11. Subcutaneous tocilizumab (Actemra) for the treatment of adult rheumatoid arthritis**

### **Application**

- 11.1. The Committee considered an application from Roche Products (New Zealand) Limited to fund subcutaneous tocilizumab (Actemra) in the community as a last-line treatment for adult patients with rheumatoid arthritis.

### **Recommendation**

- 11.2. The Committee **recommended** that subcutaneous tocilizumab (Actemra) be listed on the Pharmaceutical Schedule subject to the following Special Authority criteria, with a low priority:

#### **Special Authority for Subsidy**

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

Either:

1 All of the following:

1.1 The patient has had an initial Special Authority approval for etanercept and/or adalimumab for rheumatoid arthritis; and

1.2 Either:

1.2.1 The patient has experienced intolerable side effects from adalimumab and/or etanercept; or

1.2.2 The patient has received insufficient benefit from at least a three-month trial of adalimumab and/or etanercept such that they do not meet the renewal criteria for rheumatoid arthritis; and

1.3 The patient has been started on rituximab for rheumatoid arthritis in a DHB hospital in accordance with the HML rules; and

1.4 Either:

1.4.1 The patient has experienced intolerable side effects from rituximab; or

1.4.2 At four months following the initial course of rituximab the patient has received insufficient benefit such that they do not meet the renewal criteria for rheumatoid arthritis; or

2 All of the following:

- 2.1 Patient has had severe and active erosive rheumatoid arthritis for six months duration or longer; and
- 2.2 Tocilizumab is to be used as monotherapy; and
- 2.3 Either:
  - 2.3.1 Treatment with methotrexate is contraindicated; or
  - 2.3.2 Patient has tried and did not tolerate oral and/or parenteral methotrexate; and
- 2.4 Either:
  - 2.4.1 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of cyclosporin alone or in combination with another agent; or
  - 2.4.2 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of leflunomide alone or in combination with another agent; and
- 2.5 Either:
  - 2.5.1 Patient has persistent symptoms of poorly controlled and active disease in at least 20 active, swollen, tender joints; or
  - 2.5.2 Patient has persistent symptoms of poorly controlled and active disease in at least four active joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and
- 2.6 Either:
  - 2.6.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
  - 2.6.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

**Renewal** only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

- 1 Either:
  - 1.1 Applicant is a rheumatologist; or
  - 1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with tocilizumab treatment; and
- 2 Either:
  - 2.1 Following 6 months' initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
  - 2.2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; and
- 3 Tocilizumab to be administered at doses no greater than 162 mg every 7 days.

11.3. 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.*

## Discussion

- 11.4. The Committee noted that intravenous (IV) tocilizumab (Actemra) is currently listed on the Hospital Medicines List (HML) for use in DHB hospitals as a last-line biologic treatment for rheumatoid arthritis; as a first-line biologic treatment for rheumatoid arthritis in patients who cannot take methotrexate; as a first-line biologic treatment for systemic juvenile idiopathic arthritis (sJIA); and as a first- or second-line biologic treatment for adult-onset Still's disease.
- 11.5. The Committee noted that a subcutaneous (sc) delivery formulation of tocilizumab is now registered with Medsafe and the supplier, Roche Products (New Zealand) Limited, is seeking community funding for this formulation, in its registered indication only. The Committee noted that the sc formulation of tocilizumab is only registered for the treatment of moderate to severe active rheumatoid arthritis in adult patients, whereas

the IV formulation is registered for use in adult rheumatoid arthritis, sJIA and polyarticular JIA.

11.6. The Committee noted that the main supporting evidence for tocilizumab sc comes from the SUMMACTA trial (Burmester et al. *Ann Rheum Dis* 2014;73:69-74):

- This was a two-year, randomised, double-dummy, active-controlled, parallel-group, phase III multicentre trial in patients with rheumatoid arthritis with an inadequate response to disease modifying antirheumatic drugs (DMARDs). The study had a double-blind period of 24 weeks followed by an open-label period of 72 weeks. During the double-blind period, patients were randomly assigned 1:1 to receive 162 mg of tocilizumab sc per week plus placebo IV every 4 weeks or tocilizumab IV 8 mg/kg every 4 weeks plus placebo sc weekly for 24 weeks.
- The primary outcome was to demonstrate the non-inferiority of sc to IV tocilizumab with regard to the proportion of patients in each group achieving American College of Rheumatology (ACR)20 response at week 24, using a 12% non-inferiority margin. Secondary outcomes were disease activity score using 28 joints (DAS28), ACR responses, health assessment questionnaire scores (HAQ-DI) and safety assessments.
- A total of 1262 patients were randomly assigned, 631 received tocilizumab sc plus placebo IV and 631 received tocilizumab IV plus placebo sc. The per-protocol population, which was used for the primary, secondary and subgroup analyses, comprised 1095 patients (558 patients in the tocilizumab sc/placebo IV group and 537 patients in the tocilizumab IV/placebo sc group).
- At week 24, 69.4% (95% CI 65.5 to 73.2) of patients in the tocilizumab sc/placebo IV group achieved an ACR20 response compared with 73.4% (95% CI 69.6 to 77.1) of patients in the tocilizumab IV/placebo sc group. The difference between groups was -4.0% (95% CI -9.2 to 1.2), which was within the non-inferiority margin. ACR20, ACR50 and ACR70 response rates over 24 weeks were similar between groups as was the proportion of patients who achieved DAS28 remission over 24 weeks.
- The safety profile was similar between groups, except for more injection site reactions in the tocilizumab sc/placebo IV group.

11.7. The Committee noted the results of a smaller trial comparing fortnightly sc with 4-weekly IV tocilizumab (Ogata et al. *Arthritis Care Res* 2014;66:344-54):

- This was a double-blind, parallel-group, double-dummy, comparative phase III study in Japanese patients with rheumatoid arthritis with an inadequate response to synthetic and/or biologic DMARDs. A total of 346 patients were randomised to receive tocilizumab sc 162 mg every 2 weeks (n=173) or tocilizumab IV 8 mg/kg every 4 weeks (n=173). The primary end point was ACR20 response rates at week 24 using an 18% noninferiority margin. The per-protocol population was used for the efficacy assessments (159 patients in the tocilizumab sc group and 156 patients in the tocilizumab IV group).
- The ACR20 response rate at week 24 was 79.2% (95% CI 72.9, 85.5) in the tocilizumab sc group and 88.5% (95% CI 83.4, 93.5) in the tocilizumab IV group. The weighted difference was -9.4% (95% CI -17.6, -1.2) which was within the non-inferiority margin. Remission rates of the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate and the Clinical Disease Activity Index at week 24 were 49.7% and 16.4% in the tocilizumab sc group and 62.2% and 23.1% in the tocilizumab IV group, respectively. Incidences of all adverse events and serious adverse events were similar between groups.

- 11.8. The Committee noted the results of the BREVACTA study, a multicenter, phase III, randomised, double-blind, placebo-controlled, parallel-group trial, with a double-blind period of 24 weeks followed by an open-label period of 72 weeks (Kivitz et al. *Arthritis Care Res* 2014;66:1653-61):
- Patients with rheumatoid arthritis who had an inadequate response to DMARDs were randomised 2:1 to receive tocilizumab sc 162 mg (n=437) or placebo (n=219) every two weeks for 24 weeks. At week 24, ACR 20 was achieved in 60.9% of tocilizumab sc patients and 31.5% of patients in the placebo group;  $p < 0.0001$ . Tocilizumab was superior to placebo on all secondary end points.
  - Adverse events and serious adverse events were similar between groups. More injection site reactions occurred in the tocilizumab sc group (7.1% versus 4.1% in the placebo group). No anaphylaxis or serious hypersensitivity reactions occurred. Three patients died, all in the tocilizumab sc group; all deaths were reported as related to tocilizumab treatment. One patient died from *Hemophilus influenzae* sepsis, one from sepsis (likely from gastrointestinal causes), and one from a lower respiratory tract infection and subsequent complications.
- 11.9. Overall, the Committee considered that there was good quality evidence to support the non-inferiority of tocilizumab sc 162 mg weekly to tocilizumab IV 8 mg/kg every 4 weeks in adult patients with rheumatoid arthritis. The Committee considered that there was reasonable quality evidence supporting the use of tocilizumab sc 162 mg fortnightly, although the efficacy may be slightly lower with the longer dosing frequency. The Committee noted that the recommended dosing schedule for tocilizumab sc on the Medsafe datasheet is weekly injections of 162 mg. The Committee noted that there have been no trials comparing tocilizumab sc with other biologic agents.
- 11.10. The Committee considered that the evidence supported a similar safety profile for tocilizumab sc and IV, although the sc formulation appeared to be associated with more injection-site reactions.
- 11.11. The Committee noted the results of the SUMMACTA continuation study up to 97 weeks (Burmester et al. *Ann Rheum Dis* 2015;June 8:207281 [Epub ahead of print]). The study design included a cross-over at 24 weeks, where patients in each arm were re-randomised to receive tocilizumab sc or IV, with continuation up to 2 years. Clinical responses were sustained from week 24 to week 97 and comparable across all treatment groups. Safety profiles in patients who switched formulations were similar to those who received only tocilizumab sc or IV.
- 11.12. The Committee noted that pharmacokinetic data from the supplier suggested that tocilizumab sc has significantly lower maximum plasma concentrations and a 5-6 fold difference in the area under the curve compared with tocilizumab IV, and queried whether this could result in variation in response. In addition, there was considerable variability in the range: AUC<sub>0-168hr</sub> was 5,505 µg h/ml (SD 2,632) on day 48 after weekly sc injection of 162 mg, but with a range of 1,944 – 11,861 µg h/ml. For the fortnightly sc dose, AUC<sub>0-336hr</sub> was 2,332 µg h/ml (SD 1,696) (day 73) with a range of 172 – 6,015 µg h/ml (Zhang et al. *Int J Clin Pharmacol Ther.* 2013;51:620-30).
- 11.13. The Committee queried whether the fixed dosing regimen of the sc formulation would result in heavier patients (such as those weighing more than 100 kg) being underdosed. The Committee also noted that the low average bioavailability of the sc formulation (48% overall) and the variability of bioavailability between patients could result in some patients being underdosed.
- 11.14. The Committee considered that access to hospital infusion services was likely a barrier to some patients who meet the tocilizumab IV criteria and could benefit from treatment (e.g. rural patients), noting that the use of tocilizumab IV appeared to be inconsistent across different DHBs. The Committee considered it likely that currently such patients

would continue to receive community funded treatments (DMARDs or the biologic treatments adalimumab and etanercept) despite receiving suboptimal benefit. The Committee noted that Māori and Pacific peoples generally have less access to healthcare and so may be disproportionately affected by the requirement for tocilizumab IV to be delivered in DHB hospitals.

- 11.15. The Committee considered that aside from the hospital infusion service capacity issues, which it is possible for DHBs to manage and is not specific to tocilizumab, the key benefit of tocilizumab sc was convenience for patients and clinicians in terms of administration and dosing regimen. The Committee was uncertain as to whether tocilizumab sc would improve compliance, noting that compliance would potentially be easier to monitor with the IV formulation.
- 11.16. The Committee noted the method used by the supplier to calculate the proposed price for tocilizumab sc, with reference to the current IV pricing. The Committee considered that it was not reasonable to include IV wastage in the calculation, noting that DHB hospitals have ways of managing wastage. The Committee noted that there was significant potential for wastage of the sc preparation due to incorrect handling by the patient (e.g. leaving it out of the fridge for more than 8 hours).
- 11.17. The Committee considered that the supplier's estimates around infusion service savings were reasonable. The Committee considered that the supplier had underestimated the costs of nursing education time for tocilizumab sc and this should be closer to an hour of nursing time cost.
- 11.18. The Committee considered that the supplier had significantly underestimated the number of patients likely to take tocilizumab sc if it was funded. The Committee considered that the availability of tocilizumab sc would result in patients moving from other biologic treatments on to tocilizumab faster. The Committee considered that it was possible that up to 20% of patients currently on adalimumab or etanercept would switch to tocilizumab sc if it was available in an attempt to improve treatment response. The Committee considered it could be useful to obtain the view of the Rheumatology Subcommittee regarding this assumption. The Committee also considered that an increase in the number of readily accessible biologic treatment options would increase the total number of patients with rheumatoid arthritis on biologic treatments by up to 10% due to patients staying on a biologic treatment for longer.
- 11.19. The Committee noted that the difference in patent expiries between the sc and IV tocilizumab formulations coupled with the potential for overall biologic market growth could pose a significant fiscal risk given the current high expenditure on biologic treatments.

## **12. Tocilizumab for AA amyloidosis**

### **Application**

- 12.1. The Committee reviewed an application from a clinician for the funding of tocilizumab for the treatment of AA amyloidosis

### **Recommendation**

- 12.2. The Committee considered there was insufficient evidence to progress a Schedule listing to widen access to tocilizumab in Section H of the Pharmaceutical Schedule for the treatment of AA amyloidosis. The Committee **recommended** tocilizumab for AA amyloidosis be considered on an individual patient basis via the Named Patient Pharmaceutical Assessment (NPPA) policy with strict criteria in place for any renewal.
- 12.3. 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; vi) The budgetary impact (in terms of the pharmaceutical budget and the Governments overall health budget) of any changes to the Pharmaceutical Schedule.*

## **Discussion**

- 12.4. The Committee noted AA amyloidosis is an uncommon, but well recognised, complication of chronic inflammatory disorders. Members noted tocilizumab may be useful for AA amyloidosis because blockade of the IL-6 pathway inhibits the synthesis of inflammatory proteins such as C-reactive protein (CRP) and serum amyloid protein (SAA) by the liver. Sustained production of SAA is likely required for the development of AA amyloidosis.
- 12.5. The Committee noted AA amyloidosis is likely to be a very rare condition in New Zealand, with reported incidence of 1 to 2 per million per year from international studies (Real du Asúa et al. *Clinical Epidemiology* 2014;6:369-77). Members noted in recent cases series 40 to 50% of cases were secondary to Rheumatoid Arthritis or Ankylosing Spondylitis; and in older case series up to 50% of cases were due to chronic infection. Members noted that many epidemiological studies were conducted before the generalised use of biologic therapies for severe inflammatory arthritis and current treatment protocols probably lead to more effective control of the inflammatory process. Members noted PHARMAC has received one CEC application for anakinra for a patient on dialysis with AA amyloidosis and no NPPA applications for this indication.
- 12.6. The Committee noted organ manifestations of AA amyloidosis are variable, can be life-threatening, and could include cardiac failure, renal failure, malabsorption, and bleeding. Proteinuria is likely an early indication of renal manifestations. Diagnosis is by a history of relevant organ failure in a patient with systemic inflammation and demonstration of AA amyloid by appropriate tissue biopsy. Members noted treating the underlying disease may slow or reverse the amyloidosis, however prognosis remains poor.
- 12.7. Members noted a report from the ANZ renal replacement registry, 1960 to 2010, that found that 0.8% of all those needing renal replacement therapy had amyloidosis; however AA amyloidosis is only a sub-set of this and the registry couldn't distinguish the different types (Tang W et al. *Nephrol Dial Transplant* 2013;28:455). Members noted this is similar to the 0.8% of renal biopsies reported from a French centre (Chevrel et al. *Rheumatology* 2001;40:821-5) that showed amyloidosis, of whom rheumatoid arthritis (RA) was the most common single diagnosis (28%).
- 12.8. The Committee considered the evidence available to be of weak strength and poor quality, limited to small case studies, small retrospective cohort studies and one small prospective cohort study. There are no randomised controlled studies comparing different treatments.
- 12.9. The Committee noted the largest retrospective cohort study by Okuda et al. (*Modern Rheumatology* 2013 doi 10.1007/s10165-013-0846-7) is of 42 patients, of which 39 had RA, 2 juvenile idiopathic arthritis (JIA) and one patient had adult onset Still's disease. All patients had received one or more forms of anti-cytokine treatment; 31 with a single agent, 10 had received two agents and one had received three agents. Twenty-two patients received tocilizumab and 32 patients received a TNF-inhibitor (20 etanercept, 10 infliximab and 2 adalimumab). SAA levels reduced on both therapies and the eGFR did not change substantially. Members noted the analysis does not account for the paired nature of some of the data and therefore it is difficult to make any conclusions from this study.
- 12.10. Members noted the largest prospective cohort study (Miyagawa et al. *Modern Rheumatology* 2014;24:405-9) of five patients with a long duration of RA with either intolerance of DMARDs or active disease on etanercept and who had either proteinuria

or diarrhoea. Patients were given a year of monthly tocilizumab. Four of the five patients had reduction in proteinuria and SAA and RA disease activity improved.

- 12.11. The Committee also noted other the recent case reports by Courties et al. (Amyloid 2015; Early online publication 1-9); Magro-Checa C et al. (Amyloid 2011;18:235-9); Matsui et al. (Case reports of Nephrology 2014 Published online August 14. Article ID 823093) and Cañas-Ventura et al. (Dig Dis Sci 2013;58:2736-7).
- 12.12. Members noted AA amyloidosis does not appear to have a well-established treatment and there is an unmet health need for a small number of patients with severe uncontrolled systemic AA amyloidosis. The Committee considered that the limited evidence for AA amyloidosis means it is not possible to know if any of the suggested therapies (steroids, other immunosuppressants, TNF-inhibitors) are likely to have the same or similar effect to tocilizumab. The Committee considered that if tocilizumab controlled inflammation this could be associated with controlling AA amyloidosis, however the current evidence is too weak to be certain of this. The Committee considered that given AA amyloidosis is a rare disease there is unlikely to be high quality head-to-head trials available in the future.
- 12.13. The Committee noted there would likely be some overlap with patients who have an underlying condition associated with AA amyloidosis and it is possible these patients could access tocilizumab or TNF-inhibitors if they met the Special Authority or Hospital Medicines List criteria for their underlying condition (i.e. RA, JIA or adult onset Still's disease).
- 12.14. The Committee noted the patients most likely to benefit are those patients with severe uncontrolled inflammation associated with RA or other inflammatory arthritis with organ failure consistent with biopsy proven AA amyloidosis, and who haven't tolerated DMARDs with or without TNF-inhibitors to control the inflammation. The Committee considered that this would be a small patient group, comprising of approximately 6 patients per year. It was considered however that AA amyloidosis is an underdiagnosed condition. Members noted there was no specific information available on Maori or Pacific people with AA amyloidosis.
- 12.15. The Committee considered that patients with systemic AA amyloidosis who have not responded to other treatments and who require tocilizumab would have unique clinical characteristics and therefore consideration via the NPPA policy would be the most appropriate mechanism. Members considered strict renewal criteria would need to be established prospectively relevant to individual patient circumstances.

### **13. Rituximab for resistant nephrotic syndrome**

#### **Application**

- 13.1. The Committee reviewed an application from a clinician requesting the current hospital restrictions for rituximab be widened to include patients with idiopathic nephrotic syndrome (INS).

#### **Recommendation**

- 13.2. The Committee **recommended** that access to rituximab in Section H of the Pharmaceutical Schedule be widened to include children with steroid dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS) with a medium priority subject to the following restrictions:

Initiation – Steroid dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS).

Nephrologist

Limited to 4 weeks' treatment

All of the following:

1. Patient is a child with SDNS or FRNS; and
2. Treatment with steroids for at least a period of 3 months has been ineffective or associated with evidence of steroid toxicity; and
3. Treatment with ciclosporin for at least a period of 3 months has been ineffective; and
4. The total rituximab dose used would not exceed the equivalent of 375 mg/ m<sup>2</sup> of body surface area per week for a total of 4 weeks.

Continuation - Steroid dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS).

Nephrologist

Limited to 4 weeks' treatment

All of the following:

1. Patient who was previously treated with rituximab for nephrotic syndrome; and
2. Treatment with rituximab was previously successful and has demonstrated sustained response for >6 months, but the condition has relapsed and the patient now requires repeat treatment; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/ m<sup>2</sup> of body surface area per week for a total of 4 weeks.

- 13.3. The Committee **recommended** that access to rituximab in Section H of the Pharmaceutical Schedule be widened to include children with steroid resistant (SRNS) patients with a low priority subject to the following access restriction:

Initiation – Steroid resistant nephrotic syndrome (SRNS)

Nephrologist

Limited to 4 weeks' treatment

All of the following:

1. Patient is a child with SRNS where treatment with steroids and ciclosporin for at least a period of 3 months have been ineffective; and
2. Treatment with tacrolimus for at least a period of 3 months has been ineffective; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/ m<sup>2</sup> of body surface area per week for a total of 4 weeks.

Continuation - Steroid resistant nephrotic syndrome (SRNS)

Nephrologist

Limited to 4 doses of treatment

All of the following:

1. Patient who was previously treated with rituximab for nephrotic syndrome; and
2. Treatment with rituximab was previously successful and has demonstrated sustained response for >6 months, but the condition has relapsed and the patient now requires repeat treatment; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/ m<sup>2</sup> of body surface area per week for a total of 4 weeks.

- 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; (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 the minutes and recommendation of the Nephrology Subcommittee of PTAC meeting in December 2014. The Committee noted that Nephrotic syndrome (NS) is a disorder of the glomeruli in which excessive protein is excreted in the urine which typically leads to hypoalbuminaemia, oedema and generalised hyperlipidaemia. Members noted the presentation, disease progression and prognosis of NS is different between children and adults. The Committee noted the

Nephrotic Syndrome (NS) is classified on the basis of microscopy into minimal change disease (MCD), focal segmental glomeruli syndrome (FSGS), and membranous nephropathy (MN). MCD mostly occurs in children (85% of NS occurs in young children) and corticosteroid treatment is able to induce remission in most children and adults (more than 90%). FSGS patients comprises of 10-15% of all cases of NS in children (Greenbaum et al., Nat. Rev. Nephrol. 2012;8:445-58), however a considerable number of children with FSGS do not respond to corticosteroid treatment and it can lead to end-stage renal disease (ESRD).

- 13.6. The Committee noted that further classification of the disease in these patients is based on response to treatment, namely steroid resistant (SRNS), frequently relapsing (FRNS), and steroid-dependent (SDNS) nephrotic syndrome. The Committee also noted that although SRNS patients represent a small fraction of all paediatric nephrotic syndrome cases, it contributes disproportionately to ESRD. Failure to respond clinically to either corticosteroids or alternative treatments results in a greatly increased risk of ESRD (>50% within 4 years of diagnosis of SRNS) (Greenbaum et al., Nat. Rev. Nephrol. 2012;8:445-58) and consequently mortality.
- 13.7. The Committee considered the evidence in support of the application was mainly in children and consisting of small randomised controlled trials (RCTs) or non-experimental cohort studies of moderate strength and low quality in SDNS and FRNS, and of weak strength and low quality in SRNS. The Committee also considered that there was significant variability in follow-up times and reporting of primary outcome(s) in the studies, including percentage change in proteinuria, achieving complete and partial remission, occurrence of relapse and reduction in total corticosteroid dosing.
- 13.8. The Committee noted an open label RCT by Magnasco et al. (J Am Soc Nephrol 2012;23:1117-24) which compared 2 doses of rituximab over 2 weeks (375mg/m<sup>2</sup>) versus standard care in 31 paediatric patients with idiopathic nephrotic syndrome (INS) (23% MCD, 61% FSGS) refractory to a combination of prednisone and calcineurin inhibitors (tacrolimus 15%, ciclosporin 85%). Members noted that the primary outcome measured was percentage change in proteinuria (-12%, 95% CI -73% to 110%, p=0.77), which showed no change at 3 month follow-up.
- 13.9. The Committee noted two non-experimental studies for SRNS (Gulatti et al. Clin J Am Soc Nephrol 2010;5 2207-12; Ito et al. Pediatr Nephrol 2013;28:257-64). Members noted these studies included patients who had previously used corticosteroids, and immunosuppressants such as mycophenolate mofetil, cyclophosphamide, tacrolimus, mizoribine, and ciclosporin. The Committee noted the Gulatti et al. 2010 study of 57 patients reported 9/33 (27%) patients with SRNS had complete remission six months after rituximab therapy, 7/33 (21%) had partial remission, 17/33 (52%) patients had no response. At a mean follow-up of 21.5 months remission was sustained in 15/33 (45%) patients. In patients with SDNS, remission was sustained in 20/24 (83%) patients at 12 months, and 17/24 (71%) at mean follow up of 16.8 months.
- 13.10. The Committee noted the Ito et al. 2013 retrospective cohort study of 74 patients who received rituximab for treatment resistant NS showed 41/53 (77%) patients with SDNS/FRNS and 5/17 (29%) patients with SRNS successfully discontinued prednisolone. Ciclosporin was discontinued in 18/30 (60%) patients with SDNS/FRNS and in 1/11 (9%) of the SRNS patients. Relapse occurred at a mean of six months in 28/55 (51%) of those with SDNS/FRNS and the remaining 27/55 (49%) patients were steroid free at 17.3 months. Complete Response (CR) was achieved in 6/17 (35%) SRNS patients and partial response (PR) was achieved by 6/17 (35%) SRNS patients. Members noted significantly less relapses occurred if immunosuppressive agents were continued after rituximab (relapse occurred in 15/40 (38%) vs. 13/15 (87%); p=0.006).
- 13.11. The Committee noted the two RCT's evaluating rituximab in SDNS/FRNS by Iijima et al. (Lancet 2014;384:1273-81) and Ravani et al. (Clin J Am Soc Nephrol 2011;6:1308-15).

Members noted an open-label RCT (Iijima et al 2014) which compared rituximab (375 mg/m<sup>2</sup>, max 500mg) versus placebo once weekly for 4 weeks in 52 patients aged ≥2 years with FRNS or SDNS. Members noted that the primary outcome measured was relapse free period, which was significantly longer in the rituximab group (267 days, 95% CI 223–374) compared to the placebo group (101 days, 95% CI 70–155; HR 0.27, 95% CI 0.14–0.53; p<0.0001). All patients in the trial had relapsed after 19 months. The steroid daily dose was significantly lower with rituximab treatment (19.1 mg versus 8.37 mg, p<0.0001), but not in the placebo arm (18.02 mg versus 21.02 mg, p= 0.21). Members noted an open label RCT (Ravani et al. 2011) in 44 children with INS dependent on steroids and calcineurin inhibitors for more than 12 months comparing standard of care to rituximab (375 mg/m<sup>2</sup> intravenously; once or twice if symptoms of toxicity of steroids and/or ciclosporin) with reduced doses of prednisone and calcineurin inhibitors. Members noted that the primary outcome of proteinuria measured at 3 months, was 70% (95% CI 35-86%) lower in the rituximab group compared with standard therapy group. Relapse rates were 19% in the rituximab group and 48% in the standard therapy group (p=0.03). Members noted 63% of the rituximab group was able to stop prednisone and calcineurin inhibitors at three months compared to 4% in standard therapy group (p=0.001). Approximately 50% of the rituximab group patients were in remission without any treatment after 9 months.

- 13.12. The Committee considered three small retrospective cohort non-experimental studies in patients with SDNS previously treated with corticosteroids and or immunosuppressants (Kemper et al. *Nephrol Dial Transplant* 2012;27:1910-5; Tellier et al. *Pediatric Nephrol* 2013;28:911-18; and Sinha et al. *Ped Nephrology* 2013;80:105-13). Tellier et al. 2013 and Sinha et al. 2013 studies were in children. Members noted Kemper et al. 2012 showed rituximab was effective in reducing corticosteroid use, and repeat dosing increased time to first relapse (10.3±3.5 months in 16 patients receiving 1-2 doses vs. 23.3±18.7 months in 11 patients receiving 3-4 doses (p<0.05)). Members noted Tellier et al 2013 showed rituximab was effective in maintaining remission in 78% of patients, and increased the duration of remission in all other patients. Members also noted the study by Sinha et al. 2013 comparing patients treated with tacrolimus (13) versus rituximab (10) and followed for 12 months. Both groups had a decline in number of relapses (3.5±1.6 to 0.9±1.1; 3.1±1.1 to 0.8±1.0; p<0.001) and reduction in total prednisolone dosing.
- 13.13. The Committee considered a number of reviews on NS in paediatric patients by Sinha et al. *Ped Nephrology* 2013;80:105-13; Greenbaum et al., *Nat. Rev. Nephrol.* 2012;8: 445-58; Tullus & Marks, *Ped Nephrol* 2013;28:1001-1009; and KDIGO guidelines 2012;8:143-85. Members noted that the reviews showed little supporting evidence for rituximab, but indicated that a sub-group of paediatric patients would likely benefit from rituximab and more RCT's were needed to determine the role of rituximab in the treatment of NS.
- 13.14. The Committee noted that although the evidence suggests that rituximab would be more effective children with SDNS and FRNS, children with SRNS would benefit the most from the treatment as they have the greatest clinical need with the highest risk of progressing to ESRD. Members noted data from the Australia and NZ Paediatric Nephrology Association study (McDonald et al., *NEJM* 2004;350:2654-62) looking at long-term survival of 1,634 children aged <20 at the time of ESRD onset, who were followed for 9.7 years, showed that the long-term survival rate among children requiring renal-replacement therapy was 79% at 10 years and 66% at 20 years. Mortality rates were 30 times higher compared to children without ESRD.
- 13.15. The Committee estimated there would be less than 10 children in New Zealand with nephrotic syndrome that would require treatment with rituximab. Members noted a New Zealand population study by Wong et al. (*J Paeds Child Health* 2007;43:337-41) indicates that the rates of NS in Maori and Pacific children are comparable with census ethnicity data.

- 13.16. The Committee noted that access for rituximab in NS should be restricted to children. The Committee considered there was insufficient evidence to support the use of rituximab in adult with NS. The Committee also considered there should be separate criteria for SRNS and SDNS/FRNS patients as the quality of evidence is different for each type of NS. Members noted the PHARMAC analysis would need to be updated with child specific data in regards to patient numbers, dosing and life expectancy on dialysis.
- 13.17. The Committee noted that a four dose course was appropriate and duration of effect until relapse would be approximately nine months. Members noted that the applicant estimated that 25% of paediatric SRNS patients treated with tacrolimus would require treatment with rituximab, and that widening access for rituximab to these patients would result in approximately 20% of these patients delaying or avoiding dialysis.
- 13.18. The Committee noted that rituximab would have a role in steroid dose reduction, and in delaying ESRD. Members also noted evidence for rituximab in preventing the need for eventual dialysis is weak; however there is a significant health need and that delaying ESRD would be crucial for these patients.
- 13.19. The Committee considered that this treatment was already an established practice at some DHB hospitals prior to the introduction of the Hospital Medicines List and some patients are currently accessing treatment via the NPPA policy. Members noted that widening access to children with NS would not create any significant changes in health care expenditure, and that an assumption of 20% of total patients avoiding dialysis per year was reasonable.
- 13.20. Members noted tacrolimus was listed on the Pharmaceutical Schedule for patients with SRNS refractory or intolerant to ciclosporin from 1 August 2015. Members noted tacrolimus is not currently funded for SDNS or FRNS, therefore this patient group may require rituximab earlier in their treatment pathway.
- 13.21. The Committee considered there needs to be a persistent response for more than six months in order to access a repeat course of rituximab (to a maximum of 4 doses per course).

#### **14. Paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin for the treatment of chronic hepatitis C genotype 1<sup>1</sup>**

- 14.1. The Committee considered an application from AbbVie Limited for the funding of paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (PROD) for the treatment of chronic hepatitis C genotype 1 infection in adults.

#### **Recommendation**

- 14.2. The Committee **recommended** that paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (PROD) should be funded for the treatment of chronic hepatitis C genotype 1 infection in adults with a low priority based solely on fiscal risk.
- 14.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

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<sup>1</sup> Please note: When discussing the combination product paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (brand name Viekira Pak) the Committee used the abbreviation PROD.

## Discussion

- 14.4. The Committee noted that PROD consists of paritaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor that is required for proteolytic cleavage of HCV proteins, ombitasvir, a HCV NS5A inhibitor required for viral replication, and dasabuvir, a HCV RNA-dependent RNA polymerase inhibitor (NS5B inhibitor) that catalyses the replication of the viral RNA. In addition to these direct-acting antiviral agents (DAA), PROD also contains ritonavir, a protease inhibitor which inhibits host enzymes from metabolising paritaprevir.
- 14.5. The Committee noted that PROD is indicated for the treatment of genotype 1 chronic hepatitis C infection, including those patients who have compensated cirrhosis. The Committee noted that there is a contraindication in patients with Child-Pugh class C hepatic impairment, which includes decompensated cirrhosis. The Committee considered that in New Zealand, HCV genotype 1 makes up approximately 57% of the hepatitis C cohort. The Committee noted that PROD does not have an indication for any other genotypes of HCV, but it considered that there is some data to support the use of PROD without dasabuvir in HCV genotype 4 (Hezode et al. *Lancet*, 2015:385:2502). The Committee considered that HCV genotype 4 makes up approximately 0.5% of the New Zealand hepatitis C cohort. There is no evidence for a role in genotype 3, which make up approximately 35% of the New Zealand cohort (Lawitz et al. *J of Infect*, 2015: 70:197).
- 14.6. The Committee noted the SAPPHIRE I trial (Feld et al. *N Engl J Med*, 2014:370:1594-1603), a phase 3, multicentre, randomised, placebo-controlled, double-blind (followed by open label) study to investigate the efficacy and safety of paritaprevir/ritonavir, ombitasvir, dasabuvir + ribavirin fixed dose combination in treatment naive, non-cirrhotic, adult patients with chronic hepatitis C, genotype 1 infection. The Committee noted that the study observed 631 patients who were randomly assigned in a 3:1 ratio into one of the two groups:
- Treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD, ribavirin (weight based dosing) for 12 weeks.
  - Placebo for 12 weeks.
- 14.7. The Committee noted that the percentage of patients in the treatment group who had a sustained virologic response at 12 weeks after the end of treatment (the SVR12 rate) was 96.2% (genotype 1a – 95.3%, genotype 1b – 98%) with a 95% confidence interval of 94.5-97.9%.
- 14.8. The Committee noted the SAPPHIRE II trial (Zeuzem et al., *N Engl J Med*, 2014: 370:1604-14), a phase 3, multicentre, randomised, placebo-controlled, double-blind (followed by open label) study to investigate the efficacy and safety of paritaprevir/ritonavir, ombitasvir, dasabuvir + ribavirin fixed dose combination in treatment experienced, non-cirrhotic, adult patients with chronic hepatitis C, genotype 1 infection. The Committee noted that the study observed 394 patients who were randomly assigned in a 3:1 ratio into one of the 2 groups:
- Treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD, ribavirin (weight based dosing, <75 kg=1000 mg, ≥75 kg= 1200 mg daily divided BD) for 12 weeks.
  - Placebo for 12 weeks.
- 14.9. The Committee noted that the SVR rate in the treatment group having an SVR12 was 96.3% (genotype 1a – 96%, genotype 1b – 96.7%) with a 95% confidence interval of 94.1–98.4%.

- 14.10. The Committee noted the PEARL II trial (Andreone et al., *Gastroenterology*, 2014:147:359-65), a phase 3, multicentre, randomised, open label study to evaluate the combination regimen of paritaprevir/ritonavir, ombitasvir, dasabuvir with and without ribavirin in peginterferon/ribavirin-treatment experienced, non-cirrhotic patients with chronic hepatitis C, genotype 1b infection. The Committee noted that the study observed 179 patients who were randomly assigned in a 1:1 ratio into one of the two groups:
- Group 1 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD plus ribavirin (weight based dosing, <75 kg=1000 mg, ≥75kg=1200 mg daily divided BD) for 12 weeks.
  - Group 2 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD for 12 weeks.
- 14.11. The Committee noted that the SVR12 rate of group 1 was 96.6% (95% confidence interval of 92.8–100%) and that the SVR12 rate of group 2 was 100% (95% confidence interval of 95.9–100%).
- 14.12. The Committee noted the PEARL III trial (Ferenci et al., *N Engl J Med*, 2014: 370:1983-92), a phase 3, multicentre, randomised, placebo-controlled, double-blind study to evaluate the combination regimen of paritaprevir/ritonavir, ombitasvir, dasabuvir with and without ribavirin in treatment-naive, non-cirrhotic patients with chronic hepatitis C, genotype 1b infection. The Committee noted that the study observed 419 patients who were randomly assigned in a 1:1 ratio into one of the two groups:
- Group 1 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD plus ribavirin (weight based dosing, <75kg=1000 mg, ≥75kg=1200 mg daily divided BD) for 12 weeks.
  - Group 2 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD + placebo for 12 weeks.
- 14.13. The Committee noted that the SVR12 rate of group 1 was 99.5% (95% confidence interval of 98.6–100%) and that the SVR12 rate of group 2 was 99% (95% confidence interval of 97.7–100%).
- 14.14. The Committee noted the PEARL IV trial (Ferenci et al, *N Engl J Med*, 2014: 370:1983-92), a phase 3, multicentre, randomised, placebo-controlled, double-blind study to evaluate the combination regimen of paritaprevir/ritonavir, ombitasvir, dasabuvir with and without ribavirin in treatment naive, non-cirrhotic patients with chronic hepatitis C, genotype 1a infection. The Committee noted that the study observed 305 patients who were randomly assigned in a 1:2 ratio into one of the two groups:
- Group 1 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD plus ribavirin (weight based dosing, <75kg=1000 mg, ≥75kg=1200 mg daily divided BD) for 12 weeks.
  - Group 2 – treatment - paritaprevir 150 mg / ritonavir 100 mg /ombitasvir 25 mg OD, dasabuvir 250 mg BD plus placebo for 12 weeks.
- 14.15. The Committee noted that the SVR12 rate of group 1 was 97% (95% confidence interval of 93.7–100%) and that the SVR12 rate of group 2 was 90.2% (95% confidence interval of 86.2–94.3%).
- 14.16. The Committee noted the TURQUIOSE II trial (Poordad et al, *N Engl J Med*, 2014: 370:1973-82), a phase 3, multicentre, randomised, open label study to investigate the efficacy and safety of paritaprevir/ritonavir, ombitasvir, dasabuvir + ribavirin fixed dose combination administered for 12 or 24 weeks in treatment naive and peginterferon/ribavirin-treatment experienced, compensated cirrhotic (Child-Pugh class A) adult patients with chronic hepatitis C, genotype 1 infection. The Committee noted

that the study observed 380 patients who were randomly assigned in a 1:1 ratio into one of the two groups:

- Group 1 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD plus ribavirin (weight based dosing, <75kg=1000 mg, ≥75kg=1200 mg daily divided BD) for 12 weeks.
- Group 2 – treatment - paritaprevir 150 mg / ritonavir 100 mg / ombitasvir 25 mg OD, dasabuvir 250 mg BD plus ribavirin (weight based dosing, <75kg=1000 mg, ≥75kg=1200 mg daily divided BD) for 24 weeks.

- 14.17. The Committee noted that the SVR12 rate of group 1 was 91.8% (95% confidence interval of 87.6–96.1%) and that the SVR12 rate of group 2 was 95.9% (95% confidence interval of 92.6–99.3%).
- 14.18. The Committee considered that the evidence presented was strong and of very high quality for genotype 1. The Committee noted that the six pivotal studies had large patient numbers and consistently demonstrated SVR rates in excess of 90% in treatment naive, treatment experienced, non-cirrhotic and cirrhotic patients. The Committee considered that the SVR rates were comparable to ledipasvir with sofosbuvir for genotype 1 patients.
- 14.19. The Committee considered that the appropriate comparator is with pegylated interferon in combination with ribavirin, with or without boceprevir, and that there is now extremely low use of these agents as patients are holding off until new direct-acting antiviral agents are funded. The Committee considered that, should PROD be funded, it would completely replace the use of pegylated interferon in combination with ribavirin, with or without boceprevir in genotype 1 patients who do not have a contraindication for the use of PROD.
- 14.20. The Committee considered that it is unlikely that there would be off-label prescribing of this medication for patients infected with other HCV genotypes unless evidence for the use of this treatment in these genotypes strengthened.
- 14.21. The Committee considered that the current available therapies of pegylated interferon in combination with ribavirin, with or without boceprevir, have lower efficacy, greater toxicity and require a more prolonged duration of therapy when compared to PROD. The Committee considered that newer treatments had markedly improved efficacy and tolerability and reduced treatment duration over currently funded chronic hepatitis C treatments. Some patients are currently accessing novel chronic hepatitis C treatments via clinical trials and the majority of patients who could wait were postponing treatment in the hope that access to novel agents will be available in a short timeframe.
- 14.22. The Committee considered that Māori may have higher than predicted incidence of hepatitis C, noting a slightly higher prevalence in a pilot program conducted by the Hepatitis Foundation.
- 14.23. The Committee considered that the treatment duration of PROD and reduced toxicity may allow primary care facilities to undertake treatment. The Committee considered that the availability of fibroscan would be essential for the management of hepatitis C.
- 14.24. The Committee considered that, should current treatment options remain the only funded therapy for hepatitis C, the numbers of patients who progress to end stage liver disease would continue to rise as would associated costs.
- 14.25. The Committee considered that, compared to other direct-acting antiviral agents, PROD is limited to only a subset of genotype 1 patients.

- 14.26. The Committee noted the budget impact associated with PROD. The Committee considered that the highest needs patients who have hepatitis C are:
- HCV patients with decompensated cirrhosis (all genotypes)
  - HCV patients pre/post liver transplant (all genotypes)
  - HCV patients with essential mixed cryoglobulinaemia (with associated purpuric skin rash, cryoglobulinaemic glomerulonephritis and systemic vasculitis).
- 14.27. The Committee considered that, as PROD is only effective in genotype 1 patients, does not have a role in patients with decompensated cirrhosis, and that use in a post-transplant settings are complex due to ritonavir drug interactions with immunosuppressive therapy, it therefore does not address the needs of many of the high need groups as documented above. Therefore, the Committee considered that if PROD were funded, there would still be a need for another agent to treat other genotypes and decompensated cirrhotic patients.
- 14.28. The Committee noted the EASL prioritisation of patient subgroups and considered they were similar to those described by PTAC. The Committee noted that treating all currently diagnosed New Zealanders with genotype 1 virus would not be financially possible, and considered that restrictions on PROD should be based solely on fiscal impact.
- 14.29. The Committee considered that the area of hepatitis C treatments is continuing to evolve rapidly. The Committee noted the Request for Information that PHARMAC has issued in relation to hepatitis C treatment.

## **15. Tobramycin and azithromycin for the treatment of non-cystic-fibrosis bronchiectasis**

### **Application**

- 15.1. The Committee reviewed a paper presented by PHARMAC for clarification of conflicting recommendations received from the Anti-Infective and Respiratory Subcommittees for the use of tobramycin and azithromycin in the treatment of non-cystic fibrosis bronchiectasis.

### **Recommendation**

- 15.2. The Committee **recommended** that the application for use of tobramycin for the treatment non-cystic fibrosis bronchiectasis be declined. The Committee considered that evidence of long-term efficacy in this patient setting should be submitted in order to reconsider this application.
- 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 Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*
- 15.4. The Committee **recommended** the application for azithromycin for prevention of exacerbations in adult non-cystic fibrosis bronchiectasis should be declined, noting that an alternative treatment is available for these patients.
- 15.5. The Committee **recommended** that azithromycin be funded for non-cystic fibrosis bronchiectasis in children (aged 18 or under) who have had 3 or more exacerbations of their bronchiectasis or 3 acute admissions to hospital for treatment of infective

respiratory exacerbations within a 12 month period, for a maximum treatment duration of 24 months of therapy, with a high priority.

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

## Discussion

### Tobramycin

- 15.7. The Committee noted that at its May 2015 meeting it had requested to review an application for listing inhaled tobramycin for the treatment of non-cystic fibrosis bronchiectasis. It noted that this arose in relation to the December 2014 Anti-Infective Subcommittee minutes as follows:

Record of the Pharmacology and Therapeutics Advisory Committee Meeting Held on 7 & 8 May 2015

8.21. The Committee noted the Anti-Infective Subcommittee's recommendation in paragraph 3.51 in relation to tobramycin for non-cystic fibrosis bronchiectasis; however, the Committee considered it should review this application at a future PTAC meeting.

- 15.8. The Committee noted the relevant Anti-Infective Subcommittee minutes as follows:

Record of the Anti-Infective Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 1 December 2014

#### Tobramycin

3.51 The Subcommittee noted that there were a number of NPPA applications for tobramycin for non-CF bronchiectasis. The Subcommittee also noted that tobramycin ampoules are listed on Section B of the Pharmaceutical Schedule with the following restriction:

Only if prescribed for dialysis or cystic fibrosis patient and the prescription is endorsed accordingly.

The Subcommittee noted in Part II of Section H of the Pharmaceutical Schedule, tobramycin ampoules are not restricted by indication, but by prescriber type, namely Infectious disease physician, clinical microbiologist or Respiratory physician. The Subcommittee noted that this situation may cause issues with access to tobramycin when patients are discharged from hospital.

The Subcommittee recommended that access to tobramycin ampoules be widened in the community to include non-cystic fibrosis bronchiectasis.

- 15.9. The Committee noted the August 2014 Respiratory Subcommittee minutes in relation to the use of tobramycin for non-cystic fibrosis bronchiectasis as follows:

Record of the Respiratory Subcommittee of PTAC meeting held at PHARMAC on 30 August 2014

## Tobramycin

4.15 The Subcommittee considered whether the restrictions applying to tobramycin in the hospital setting should also be applied to the community. Use in the community is currently restricted to the treatment of dialysis or cystic fibrosis patients only. The Subcommittee noted that there had been a number of Named Patient Pharmaceutical Assessments (NPPA) applications for the long term use of tobramycin in the community for patients who do not meet the current criteria.

4.16 The Subcommittee noted that currently many DHB hospitals are providing tobramycin long term into the community for patients who do not meet the community criteria.

4.17 The Subcommittee considered that if a patient has pseudomonas they should have access to tobramycin regardless of any other clinical condition they may have. The Subcommittee noted that tobramycin was more active than gentamycin against pseudomonas, some pseudomonas are resistant to gentamycin and there is a higher risk of ototoxicity with gentamycin. For these reasons, inhaled tobramycin is the treatment of choice for non-cystic fibrosis bronchiectasis followed by ceftazidime if standard treatment fails.

4.18 The Subcommittee recommended, with a high priority, that the restriction pertaining to the use of tobramycin in the community be widened to include the treatment of non-cystic fibrosis patients with bronchiectasis with pseudomonas or similar gram-negative infection and the prescription should be endorsed accordingly.

- 15.10. The Committee noted the current listings and restrictions associated with the listing of tobramycin in Section B and Part II of Section H of the Pharmaceutical Schedule.
- 15.11. The Committee noted that tobramycin is an aminoglycoside antibiotic with good in vitro activity against *P.aeruginosa*, as well as other gram negative and some gram positive aerobic bacteria. It noted that tobramycin and other aminoglycosides do not penetrate bronchial secretions when given parenterally or orally and therefore high doses are required to achieve adequate concentrations. The Committee also noted that high doses of parenteral or oral tobramycin are associated with an increased risk of nephrotoxicity and ototoxicity. The Committee noted that inhaled antibiotics allow high concentrations at the infection site to be achieved with reduced systemic absorption and risk of adverse events.
- 15.12. The Committee considered that there is good evidence to support the use of inhaled tobramycin in cystic fibrosis bronchiectasis and that it is listed on both Section B and Part II of Section H of the Pharmaceutical Schedule for this indication.
- 15.13. The Committee noted that the parenteral formulation of tobramycin is listed on Part II of Section H of the Pharmaceutical Schedule restricted to infectious disease and respiratory physicians. The Committee noted that the current restriction allowed prescribing of tobramycin for non-cystic fibrosis bronchiectasis in hospital. The Committee further noted that rule 8 of Part II of Section H of the Pharmaceutical Schedule relating to community use of hospital pharmaceuticals allows DHB Hospitals to give tobramycin injection 40 mg per ml, 2 ml vial or tobramycin injection 100 mg per ml, 5 ml vial to a patient for use in the community, provided that:
- a) the quantity does not exceed that sufficient for up to 30 days' treatment, unless:
    - i) it would be inappropriate to provide less than the amount in an original pack; or
    - ii) the relevant DHB Hospital has a Dispensing for Discharge Policy and the quantity dispensed is in accordance with that policy; and

b) tobramycin injection is supplied consistent with any applicable restrictions. In this case, that it is prescribed by an infectious disease physician, clinical microbiologist or respiratory physician.

- 15.14. The Committee noted the Named Patient Pharmaceutical Assessment (NPPA) applications for tobramycin for use in the community for non-cystic fibrosis bronchiectasis.
- 15.15. The Committee noted that the parenteral formulation of tobramycin has been extensively used for inhaled administration. The Committee noted that concerns have been raised relating to the low pH and preservative content of the parenteral formulation. The Committee noted a paper by Nikolaizik et al. (Eur Respir J 2002; 20: 122–6) relating to bronchial reactions to the inhalation of high-dose tobramycin in cystic fibrosis. The Committee noted that inhaled parenteral preparations, inhalation solutions and saline were all associated with a decline in lung function and that no significant differences were observed between the formulations with and without preservatives.
- 15.16. The Committee discussed the appropriate dose of tobramycin. It considered that the recommended dose of inhaled tobramycin for treating *P.aeruginosa* in cystic fibrosis is 300mg twice daily. It noted that this was the dosage used in the Ramsey et al. (NEJM, 1999; 340: 23-30) study; a multicentre, placebo controlled, double blind trial that demonstrated significant improvements in FEV1 and reductions in density in sputum *P.aeruginosa*, and reduced hospitalisations in patients with cystic fibrosis. However, the Committee noted PHARMAC data that suggested that the parenteral formulation was being inhaled at a dosage of approximately 160mg/day. The Committee noted a Nikolaizik et al. study (Can Respir J 2008;15; 259-62), designed to compare tobramycin 80 mg injectable preparation with 300 mg solution for inhalation in cystic fibrosis patients. The study compared 80 mg tobramycin administered twice daily over 12 weeks compared with 300 mg tobramycin administered twice daily in a 4 weekly cycle. However the Committee considered that there were significant methodological flaws with the study. The Committee noted that the study failed to demonstrate either clinical or statistical difference from baseline between the two treatments.
- 15.17. The Committee considered the evidence of efficacy for use of tobramycin in non-cystic fibrosis bronchiectasis. The Committee noted papers by Barker et al. (Am J Respir Crit Care Med. 2000;162:481–5) Scheinberg and Shore (Chest. 2005;127:1420–6), Drobnic et al. (Ann Pharmacother 2005;39:39–44), Vendrell et al. (Open Respir Med J. 2015; 9: 30–6), British Thoracic Society guideline for non-CF bronchiectasis (Thorax. 2010;65(Suppl 1):i1–58) and the 2014 Chronic Suppurative Lung Disease and Bronchiectasis in Children and Adults in Australia and New Zealand clinical guidelines from the Thoracic Society of Australia and New Zealand (accessed from <http://www.thoracic.org.au/professional-information/position-papers-guidelines/bronchiectasis/>).
- 15.18. The Committee noted that no NICE assessment on the use of tobramycin in non-cystic fibrosis bronchiectasis has been performed. It also noted that Australia, Scotland and the European Medicines Agency only recommends or funds tobramycin for use in cystic fibrosis bronchiectasis.
- 15.19. The Committee noted that there is no international consensus on the use of tobramycin for non-cystic fibrosis bronchiectasis.
- 15.20. The Committee considered that there is weak evidence of efficacy from a limited number of studies. The Committee noted that the studies were small, with variable treatment regimens and treatment durations. The Committee considered that no evidence had been presented in relation to improved lung function and quality of life changes were variable. The Committee noted that benefits of treatment were limited to reduced hospitalisation rates and reduced bacterial sputum. However, it noted that the effect of

reduced bacterial sputum was limited to the time on treatment and following treatment cessation, the sputum bacterial load subsequently increased again.

- 15.21. The Committee noted the relatively high rates of adverse effects, particularly respiratory adverse effects in non-cystic fibrosis bronchiectasis patients receiving tobramycin.
- 15.22. The Committee noted that antibiotic resistance is a potential issue associated with the use of tobramycin in non-cystic fibrosis bronchiectasis. The Committee noted that in the Barker et al. study, 11% of patients developed tobramycin-resistance compared with 3% of those who received placebo.
- 15.23. The Committee **recommended** that the application for use of tobramycin for the treatment non-cystic fibrosis bronchiectasis be declined. The Committee considered that evidence of long-term efficacy in this patient setting should be submitted in order to reconsider this application.

### **Azithromycin**

- 15.24. The Committee noted a clinician's funding application for azithromycin for non-cystic fibrosis bronchiectasis that was received in November 2013. The Committee noted that contradictory advice had been received by PHARMAC staff in relation to the application from the Anti-infective Subcommittee of PTAC and the Respiratory Subcommittee of PTAC.
- 15.25. The Committee noted azithromycin is a macrolide antibiotic that has potent anti-inflammatory properties. The Committee noted that a number of other macrolide antibiotics are funded on the Pharmaceutical Schedule.
- 15.26. The Committee noted that PHARMAC had received a total of 9 Named Patient Pharmaceutical Assessment (NPPA) applications for azithromycin for non-cystic fibrosis bronchiectasis over the past 3.5 years.
- 15.27. The Committee noted that currently azithromycin is listed in Section B of the Pharmaceutical Schedule for any condition for a maximum of 5 days treatment. The Committee noted that this maximum of 5 days treatment restriction can be waived by endorsement for patients who have received a lung transplant and require treatment or prophylaxis for bronchiolitis obliterans syndrome, or for cystic fibrosis patients who have chronic infection with *Pseudomonas aeruginosa* or *Pseudomonas* related gram negative organisms. The Committee noted that a similar restriction exists in Part II of Section H of the Pharmaceutical Schedule.
- 15.28. The Committee noted a number of studies in relation to the use of azithromycin for non-cystic fibrosis bronchiectasis including the EMBRACE trial (Wong et al. Lancet. 2012;380:660-7), the BAT trial (Altenburg et al. JAMA. 2013;309:1251-9) the BLESS trial (Serisier et al. JAMA. 2013;309:1260-7) and the study conducted in the paediatric population by Valery et al. (Lancet Respir Med, 2013; 1:610-20). The Committee also noted the TSANZ 2014 bronchiectasis guidelines.
- 15.29. The Committee considered that data from the EMBRACE and BLESS trials demonstrate significant reductions in both the rate and risk of event-based pulmonary exacerbations during azithromycin treatment for 6-12 months. The Committee noted that in the New Zealand cohort in the EMBRACE trial, these effects lasted beyond the 6 month treatment period. The Committee noted that the median time to first exacerbation was also significantly longer in the group treated with azithromycin. The Committee noted that there were no significant differences in the annual rate of symptom-based exacerbations, lung function, health-related quality of life, exercise capacity, or bacterial cell count in sputum in the azithromycin group when compared to the placebo group.

- 15.30. The Committee noted the duration of follow-up in the above trials and considered that evidence was not yet available to evaluate the long-term benefits of treatment.
- 15.31. The Committee noted that all of the trials were placebo-controlled and that no comparative trials had been presented comparing azithromycin with other macrolide antibiotics.
- 15.32. The Committee considered that there is the possibility of a higher macrolide resistance risk with azithromycin as a result of its pharmacokinetic properties. The Committee considered that this may be a class effect. The Committee noted the BLESS trial reported an increase in macrolide-resistant oropharyngeal streptococci in the erythromycin group.
- 15.33. The Committee considered the evidence presented in the Valery et al. study (Lancet Respir Med, 2013;1:610-20) for use of azithromycin for non-cystic fibrosis bronchiectasis in the paediatric population. The Committee noted that the study suggested that indigenous children who received azithromycin were significantly less likely to have a pulmonary exacerbation when compared to those on placebo. The Committee considered that a major advantage of azithromycin over alternative treatments is that it only requires once weekly dosing. The Committee considered that once weekly dosing may be amenable to directly observed therapy which would be advantageous in population groups where compliance is an issue. The Committee noted the Valery et al. study also reported fewer non-pulmonary bacterial infections in the azithromycin treatment group. The Committee considered that this may be advantageous in children who are living in low socioeconomic areas who are at increased risk of developing other bacterial infections (eg. skin and soft tissue infections).
- 15.34. The Committee considered that the high bacterial loads associated with non-cystic fibrosis bronchiectasis are associated with local and systemic inflammation and a greater risk of exacerbations. The Committee noted that chronic *P.aeruginosa* infection is associated with worse quality of life, declining lung function, and greater mortality.
- 15.35. The Committee discussed the risk of increased macrolide resistance. The Committee noted that the benefits of a longer half-life of azithromycin which allows once weekly dosing may be outweighed by the increased risk of developing macrolide resistance in nasopharyngeal flora due to being exposed to prolonged periods of sub-inhibitory antibiotic concentrations. The Committee also noted that clonal expansions of these resistant strains may increase the risk of transmission to untreated individuals in the community.
- 15.36. The Committee considered that there is an alternative therapy for non-cystic fibrosis bronchiectasis for use in adults in the form of erythromycin. The Committee considered that, in order to further consider funding for the adult population, evidence should be presented that confirms the need for azithromycin over other macrolides. The optimal dose and duration of treatment also requires clarification.
- 15.37. The Committee noted the Anti-Infective Subcommittee advice in relation to azithromycin. The Committee agreed with this recommendation; however it recommended that the following change be made to clarify the recommendation (changes in bold):

4.10 The Subcommittee recommended the application for azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis **in adults** should be declined, noting that an alternative treatment is available for these patients.

4.11 The Subcommittee recommended that short courses of azithromycin of 5 days treatment should be restricted to the following indications; mycoplasma genitalium infection when first-line treatments have failed, pertussis and chlamydia.

4.12 The Subcommittee recommended that longer courses of azithromycin should be restricted to the following indications; patients who have received a lung transplant and require treatment or prophylaxis for bronchiolitis obliterans syndrome, patients with cystic fibrosis and have chronic infection with *Pseudomonas aeruginosa* or *Pseudomonas* related gram negative organisms, mycobacterium avium intracellulare complex infections and non-cystic fibrosis related bronchiectasis in children who have had 3 or more exacerbations of their bronchiectasis or 3 acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period.

- 15.38. The Committee considered that a maximum duration of therapy should be specified. The Committee noted the maximum treatment duration in the Valery et al. study varied between 12 and 24 months with a mean of 20.7 months treatment duration. The Committee noted the Thoracic Society of Australia and New Zealand guidelines which recommend a finite duration of treatment of 12-24 months. The Committee noted the recommendation of the Anti-Infective Subcommittee who suggested an initial treatment duration of 12 months with evidence of improvement having to be demonstrated before a renewal could be issued for a further 6-12 months.
- 15.39. The Committee noted the Respiratory Subcommittees concern in relation to those patients who would be transitioning from a paediatric to an adult treatment regimen. The Committee noted this concern and considered that changes to azithromycin therapy for non-cystic fibrosis during a treatment course were not advisable. The Committee considered that this transition could be managed through an appropriate Special Authority. The Committee noted that the paediatric study populations were restricted to patients aged under 18 and considered that this is the clinically appropriate age to restrict access to this treatment.
- 15.40. The Committee noted the Twiss et al. prospective study 2001-2002 (Arch Dis Child, 2005; 90: 737-40) and considered that incidence of non-cystic fibrosis bronchiectasis disproportionately affects Māori and Pacific Island children, The Committee considered that the incidence of non-cystic fibrosis bronchiectasis in children under 15 years in New Zealand is 3.7 cases per 100,000 per year and of this group, approximately 50% would have had 3 or more exacerbations of their bronchiectasis or 3 acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period. The Committee considered that approximately 80% of this population would be Māori or Pacific Islanders.
- 15.41. The Committee **recommended** the application for azithromycin for prevention of exacerbations in adult non-cystic fibrosis bronchiectasis should be declined, noting that an alternative treatment is available for these patients.
- 15.42. The Committee **recommended** that azithromycin be funded for non-cystic fibrosis bronchiectasis in children (aged 18 or under) who have had 3 or more exacerbations of their bronchiectasis or 3 acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period, for a maximum treatment duration of 24 months of therapy, with a high priority. The Committee considered that the appropriate dosage of azithromycin for non-cystic fibrosis bronchiectasis for children would be 30mg/kg with a maximum dosage of 600mg.

## 16. Zoster Vaccine

### Application

- 16.1. The Committee reviewed a PHARMAC generated paper on the cost-utility analysis (CUA) of zoster vaccination.

### Recommendation

- 16.2. The Committee **recommended** zoster vaccination be listed on the Pharmaceutical schedule for vaccination of people aged 65 and older with a catch-up programme with a medium priority.
- 16.3. 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; (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

- 16.4. The Committee noted that it had reviewed zoster vaccination previously at its August 2014 meeting and had recommended zoster vaccine be listed on the Pharmaceutical Schedule with a medium priority. The Committee had requested PHARMAC prepare CUAs for PTAC to review covering a range of assumptions, including age-related disease burden scenarios that incorporated remaining life expectancy for specific demographic groups (hence varying need and benefit over time). The Committee requested that assumptions include a waning of vaccine efficacy over time as per current available data, and that sensitivity analysis include a possible booster at 10 years (although members did recognise that the 10-year booster scenario has no current evidence base).
- 16.5. The Committee noted a significant increase year on year in the dispensing of aciclovir 35 x 800 mg tabs in New Zealand over a five year period, particularly in those aged 50 years or age or older. The Committee noted that capsaicin cream 0.075% is fully funded by endorsement for post-herpetic neuralgia or diabetic peripheral neuropathy. The Committee noted that in 2013 and 2014, approximately 2,300 patients were dispensed capsaicin cream 0.075% without a dispensing for a diabetic product such as test strips and this data was used to determine local rates of post-herpetic neuralgia.
- 16.6. The Committee noted a published review of 130 studies conducted in 26 countries (Kawai et al. 'Systematic review of incidence and complications of herpes zoster: towards a global perspective' *BMJ Open* 2014;4:e004833). The authors reported similar age-specific rates of herpes zoster in North America, Europe and Asia-Pacific which are similar to the rates seen in New Zealand. The Authors quoted rates of 4 per 1000 population at age 50 years through to 11 per 1000 population at age 80 and again these figures are similar to those in New Zealand. The Committee noted that Kawai et al. state that 30-50% of patients who have herpes zoster develop post-herpetic neuralgia, Members noted this is higher than estimated for the New Zealand population (based on capsaicin cream claims data) but the difference may be accounted for by patients who are being dispensed capsaicin cream 0.075% having a more severe case of post-herpetic neuralgia.
- 16.7. The Committee noted that there appeared to be international evidence of an increase in incidence of herpes zoster of ~0.25/1000 over the past few years and that there was a 0.2% to 1% per year recurrence rate. The Committee noted that there was no evidence as to whether recurrent episodes were worse than or the same as the initial episode. The Committee noted from a study by Heymann et al. *Infection* 2008;36:226-30) that diabetes mellitus was associated with an increased risk of herpes zoster (OR = 1.53; 95% CI 1.44-1.62).
- 16.8. The Committee noted that there was a significant difference in the efficacy of herpes zoster vaccination dependent of the age of vaccination with efficacy of ~64% in 60-69 year olds dropping to 38% in those 70 plus. The Committee noted the Immunisation Subcommittee had not recommended a booster dose as the Subcommittee had considered that there was no evidence or information on the need for a booster

vaccination at this stage. The Committee noted there have been no controlled clinical trials using booster vaccinations and considered there was no need to model a booster dose until the evidence becomes available.

- 16.9. The Committee considered that if the zoster vaccine was not given at the same time as the influenza vaccine there would be additional costs to the health sector due to the \$20 payment for vaccination. The Committee noted that in the UK, 75% of patients received the zoster vaccine at the same time as the influenza vaccine, and 25% received the zoster vaccine outside of the influenza season. The Committee noted that there was no evidence of any effect on either vaccine if they were given concurrently.
- 16.10. The Committee considered that there is no evidence of a change in efficacy of the vaccine if the person has previously had one or more episodes of shingles.
- 16.11. The Committee considered that determination of the age of vaccination is largely a financial decision taking into account budget impact and the cost utility analysis. The Committee noted that while Zostavax is registered for use from age 50, the major clinical trials did not include patients under the age of 60 years. The Committee considered 65 was a reasonable age as that coincided with influenza vaccination however it is important to note that that efficacy decreases markedly with age. The Committee noted a recently published long term follow up of the Shingles Prevention Study by Morrison et al. ('Long-term persistence of zoster vaccine efficacy, CID 2015:60 (15 March) DOI:10.1093/cid/ciu918). The study followed 6867 Shingles Prevention Study vaccine recipients and followed them for up to 11 years. Morrison et al. reported that statistically significant vaccine efficacy for herpes zoster burden of illness persisted into year 10 post vaccination; whereas statistically significant vaccine efficacy for incidence of herpes zoster persisted only through year 8. The Committee considered PHARMAC should use this information to update the cost utility model.
- 16.12. The Committee considered that zoster vaccination at 65 years with a catch-up was the best option. The Committee recognised that while the vaccine may be more efficacious in younger age groups, there would be a significant cost associated with these age groups due to the larger numbers of people that could be vaccinated. The cost of vaccination outweighs the benefits in these age groups. As the efficacy of vaccination wanes in older age groups, the benefit of vaccination may not be achieved although the cost to the Combined Pharmaceutical Budget would be less. The Committee **recommended** PHARMAC reconfirm its cost utility model to ensure that 65 years is the most cost efficient age of vaccination.
- 16.13. The Committee **recommended** the catch-up programme should allow for all people over the age of 65 years the opportunity to receive one dose of zoster vaccine but that the time period for the catch-up programme should be limited to two years.

## **17. Pneumococcal polysaccharide vaccine (Pneumovax23) for immunisation of adults over 65 years**

### **Application**

- 17.1. The Committee reviewed a supplementary submission from Merck Sharp and Dohme for widening access to Pneumovax 23 for vaccination against pneumococcal pneumonia and invasive pneumococcal disease in adults aged 65 years.

### **Recommendation**

- 17.2. The Committee **recommended** the application to widen access to Pneumovax 23 to vaccination of all adults aged 65 years and older be declined.
- 17.3. 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; (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**

- 17.4. The Committee noted that it had first reviewed an application from Merck Sharp and Dohme (MSD) for the listing of pneumococcal vaccine polyvalent on the Pharmaceutical Schedule for the vaccination of all people in the 65 and over age group at its February 2014 meeting. The Committee noted that at that time it had considered the evidence for effectiveness of PPV23 at a population level was poor and the evidence for PPV23 in the elderly population was also poor.
- 17.5. The Committee had also considered that PPV23 would be given in conjunction with the influenza vaccine which may increase the uptake to approximately 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.
- 17.6. The Committee noted the ESR April 2015 Invasive Pneumococcal Report stated that invasive pneumococcal disease (IPD) cases increased in those aged 65 years and over from 187 in 2014 (29.9/100,000) to 215 in 2015 (33.1/100,000). Over the same period there was an increase in rates in those aged <2 years and 2-4 years. However there was a decrease in rates in those aged 5-64 years. Members noted that data by serotype combined all ages into a category of 5 years and over as one age group and this makes data interpretation difficult. Serotypes 3 and 19A increased, from 23 to 32 cases and 62 to 74 cases respectively in those aged ≥5 years. Members noted earlier rates of IPD from the ESR 2013 surveillance report for those aged ≥65 years; the rate was 33.0/100,000 in 2006, peaking at 43.6/100,000 in 2009, and 29.4/100,000 in 2013.
- 17.7. The Committee reviewed a number of studies that had not been available for the first application including Moberley et al. 2013 (Cochrane Database Syst Rev 2013(1):CD000422), Menzies et al. (Med J Aust 2014;200:112-5) ; Ochoa-Gondar et al. (Clin Infect Dis 2014;58:909-17); and Leventer-Roberts et al. (Clinical Infectious Diseases: advance access March 5, 2015).
- 17.8. The Committee noted the Moberley et al. 2013 Cochrane review considered randomised controlled trials (RCT) of vaccines for the prevention of pneumococcal infection in adults. They also considered non-RCTs in adults, where the study assessed polysaccharide pneumococcal vaccine (PPV) effectiveness against culture-confirmed invasive pneumococcal disease (IPD), provided the study controlled for important confounding factors. The objective was to assess the efficacy and effectiveness of PPVs in preventing pneumococcal disease or death in adults. The meta-analysis included 18 RCTs with 64,852 participants and seven non-RCTs with 62,294 participants.
- 17.9. Members noted most RCTs scored poorly for overall risk of bias and only 4/18 had an overall low risk of bias. Non-RCTs were all scored uncertain for complete outcome data and 3/7 uncertain for selective reporting. RCT evidence: IPD vaccine efficacy (VE)=74% (55-86%, n=36,489, I<sup>2</sup>=0%), adults with chronic disease in high-income countries IPD OR=1.56 (0.35-6.94, n=3,230, I<sup>2</sup>=0%), otherwise healthy adults in high-income countries IPD OR=0.2 (0.1-0.39, n=27,886, I<sup>2</sup>=0%). Pneumonia (all cause) OR=0.72 (0.56-0.93, n=47,734, I<sup>2</sup>=85% high level heterogeneity), adults with chronic disease in high-income countries IPD OR=0.93 (0.73-1.19, n=4,010, I<sup>2</sup>=10%), otherwise healthy adults in high-income countries IPD OR=0.71 (0.45-1.12, n=29,186, I<sup>2</sup>=93% high level heterogeneity). Mortality (all cause) OR=0.90 (0.74-1.09, n=47,560, I<sup>2</sup>=69% high level heterogeneity), adults with chronic disease in high-income countries IPD OR=1.13 (0.90-1.43, n=3,603, I<sup>2</sup>=6%), otherwise healthy adults in high-income countries IPD OR=0.88

(0.67-1.17,  $n=32,023$ ,  $I^2=79\%$  high level heterogeneity). Two RCTs used PPV23 in otherwise healthy adults in high-income countries; Maruyama et al. (BMJ 2010;340:c1004doi:10.1136/bmj.c1004) in a study of 1,008 nursing home residents aged 55-106 years, and Ortqvist (Lancet 1998;351:399-403) in a study of 691 non-immunocompromised Swedish adults 50-85 years who had been inpatients for community acquired pneumonia (CAP). Non-RCT evidence: IPD OR=0.48 (0.37-0.61, 7 studies,  $I^2=31\%$ ).

- 17.10. The Committee noted that in summary, Moberley et al. reported the meta-analysis provides evidence that PPV is protective against IPD, but no evidence in support of all cause pneumonia or mortality.
- 17.11. The Committee noted Menzies et al. (Impact of pneumococcal polysaccharide vaccine in people aged 65 years or older Med J Aust 2014;200:112-5) reported a greater reduction in IPD in the  $\geq 65$ -year-olds compared with 50-64 year-olds but the difference did not reach statistical significance. However, the vaccine effectiveness was significant. Members noted greater reductions in IPD in  $\geq 65$ -year-olds would be expected from the indirect effects of using 13-valent pneumococcal conjugate vaccines in infants and an increase in the coverage of the 23PPV vaccine.
- 17.12. The Committee noted Ochoa-Gondar et al. (Clin Infect Dis 2014;58:909-17) was a prospective population cohort study in 27,204 individuals from 9 primary care practices in Catalonia, Spain, where PPV23 has been recommended for individuals  $\geq 60$  years since 2002. At baseline 12,044 were never vaccinated at the start of the study, these individuals were younger, visited the doctor less, less likely to receive influenza vaccine and less likely to have comorbidities. No difference between vaccinated and non-vaccinated individuals were found overall in the main analysis for bacteremic pneumococcal CAP, non-bacteremic pneumococcal CAP, all-cause CAP, death from CAP, and all-cause death. However, in the subgroup ( $n=2,390$ ) vaccinated after the start of the study the multivariate adjusted pneumococcal CAP HR=0.09 (0.02-0.48) was significant, although the all-cause CAP and death from CAP were not significant. Furthermore, the findings were non-significant for all outcomes for subgroups on the basis of immune status, influenza vaccine status, nursing home residence, or in the whole cohort using the classification of ever vaccinated. In a restricted dataset analysis comparing those vaccinated within 5 years of study onset to never vaccinated bacteremic pneumococcal, the adjusted HR=0.38 (0.09-1.68); nonbacteremic pneumococcal CAP adjusted HR=0.52 (0.29-0.92); overall pneumococcal CAP adjusted HR=0.49 (0.29-0.84); all cause CAP adjusted HR=0.75 (0.58-0.98). The Committee noted that the data do need to be interpreted with caution as this is from an observational study residual confounding cannot be excluded, findings were only present in subgroup analysis, and the number of cases is numerically low.
- 17.13. Leventer-Roberts et al. (Clinical Infectious Diseases advance access March 5, 2015) reported on a retrospective cohort study of a case-control study nested in a population-based cohort. The Committee noted a retrospective case-control study using the electronic medical records of the Clalit Health Services in Israel (53% of the population, with  $\sim 500,000$  members  $\geq 65$  years, among whom  $\sim 80\%$  receive PPV23). Cases of IPD and hospital-treated pneumonia (HTP) were selected from 2008-2010. Controls were randomly selected and matched for age, sex, risk. PCV23 became standard in 2007. There were 212 patients with IPD and 23,740 with HTP. Unadjusted and adjusted OR suggested PPV23 was protective against IPD (unadjusted 0.66, 0.48-0.90; adjusted 0.58, 0.41-0.81), but not HTP. In subgroup analysis the protection against IPD was not present in those  $\geq 75$  years, while a strong protective effect was seen in those aged 65-74 years; however, an interaction p value was not given for this analysis.
- 17.14. The Committee also reviewed evidence from population modelling, International committee recommendations and clinical studies including the following studies that had also been reviewed at the February 2014 meetings:

- Dominguez et al. 'Effectiveness of the pneumococcal polysaccharide vaccine in preventing pneumonia in the elderly' *Eur Resp J* 2010;36:608-14
  - Maruyama et al. 'Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trials' *BMJ* 2010;340:c1004
  - Ortqvist et al. 'Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people' *Lancet* 1998;351:399-403
  - Vila-Corcoles et al. 'Clinical effectiveness of 23-valent pneumococcal vaccine against pneumonia in middle-aged and older adults: A matched case-control study' *vaccine* (2009;27:1504-10
  - Kawakami et al. 'Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan' *vaccine* 2010;28:7063-9
- 17.15. The Committee considered that, in summary there was high quality randomised controlled trial evidence of good affect against invasive pneumococcal disease however, the RCT evidence against either pneumococcal pneumonia or all-cause pneumonias in the general 65 years and over population was less convincing. The Committee noted one RCT (Maruyama et al. *BMJ* 2010;340:c1004) of efficacy for all-cause and pneumococcal pneumonia, and death from pneumococcal pneumonia, but not from all-cause pneumonia death or all-cause death. The Committee noted that there was RCT evidence of no efficacy in those patients who had previously been hospitalised with CAP or those attending respiratory and general medical clinics although subgroup analysis suggests there is a benefit in those aged  $\geq 75$  years and those with difficulty walking. The Committee considered there was low grade, non-experimental evidence of efficacy against IPD (including bacteremic pneumococcal pneumonia), but no evidence in primary analysis of efficacy for all-cause pneumonia, although there is sub-group evidence in those immunised <5 years previously.
- 17.16. The Committee noted that there is potential for PCV13 to be given prior to PPV23 although high quality evidence for this strategy has not been presented to the Committee for consideration. The Committee considered that the evidence presented showed PPV23 is effective against IPD but efficacy in all-cause pneumonia is questionable. The Committee considered that there was insufficient information on what percentage of pneumococcal disease in New Zealand is IPD and that it would be very difficult to target the population who may benefit most from vaccination.
- 17.17. The Committee noted that the hospitalisation rates used in the suppliers economic evaluation were taken from the Scott paper (Scott et al. 'Economic analysis of community-acquired pneumonia in New Zealand adults', *NZMJ* 2004;117(1196)) and related to the years 2000 to 2002. Scott et al. estimated that 40% of CAP patients were treated in hospital. The proportion of non-bacteremic pneumococcal pneumonia estimate of 40% was from a 20 year old Christchurch study (Neill et al. 'Community-acquired pneumonia: aetiology and usefulness of severity criteria on admission, *Thorax* 1996;51:1010-16). The Committee considered that these estimates are likely to be imprecise as the rates may have changed considerably with increased GP managed care, emergency department care and rest home care. The Committee considered that the incidence of CAP that is due to susceptible pneumococci is highly likely to have reduced in New Zealand in the past 20 years due to childhood immunisation as has been shown in the US and reported in the a study by Moore et al. (Moore et al. 'Effect of use of the 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance' *Lancet Infect Dis* 2015;15:301-9).

- 17.18. The Committee noted that the incidence of IPD in those aged 65 years and over is 3 to 4 times higher in Māori and Pacific peoples than it is in Europeans.
- 17.19. The Committee **recommended** the application to widen access to Pneumovax 23 to vaccination of all adults aged 65 years and older be declined.

## **18. Pneumococcal vaccine (Prevenar13) for immunisation of adults over 65 years**

### **Application**

- 18.1. The Committee reviewed an application from Pfizer New Zealand Ltd for widening access to Prevenar 13 for vaccination against pneumococcal pneumonia and invasive pneumococcal disease in adults aged 65 years.

### **Recommendation**

- 18.2. The Committee **recommended** the application be declined.
- 18.3. 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; (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**

- 18.4. The Committee noted that the clinical evidence for Prevenar 13 consisted of one large, randomised trial conducted in The Netherlands – the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA) (Bonten et al. NEJM 2015;72:1114-25). CAPITA was a parallel group, randomised, double-blind, placebo-controlled trial of polysaccharide conjugate vaccine (PCV 13) involving 84,496 adults over the age of 65 years. The Committee considered the vaccine and placebo groups were well matched and the population had a broadly similar prevalence of chronic health conditions to the New Zealand population and similar rates of childhood pneumococcal vaccination.
- 18.5. Of the 84,496 participants who were enrolled, 42,240 received PCV13 and 42,256 received placebo. The mean follow-up time was 3.97 years in both groups with discontinuation rates of 12.4% in the PCV13 group and 12.6% in the placebo group, primarily due to death or loss to follow up. In the PCV13 group 1,552 people visited a sentinel centre with suspected community acquired pneumonia (CAP) or invasive pneumococcal disease (IPD) versus 1,680 in the placebo group. Approximately 57% in each group had confirmed episodes of CAP or IPD and of these approximately 75% did not have pneumococcal CAP or IPD. A further 5% were excluded because of immunosuppression or immunodeficiency and a small number were excluded because of protocol violations. These patients were included in the intention to treat analysis but not the per-protocol analysis.
- 18.6. The Committee noted that analysis of the primary end-point found a first episode of confirmed vaccine-type CAP was documented in 49 participants in the PCV13 group and 90 in the placebo group (vaccine efficacy, 45.6%; 95.2% confidence interval [CI], 21.8 to 62.5;  $p < 0.001$ ). In the secondary end-point analysis, a first episode of confirmed non-bacteremic and non-invasive vaccine-type CAP was demonstrated in 33 participants in the PCV13 groups and 60 in the placebo group (vaccine efficacy in the per-protocol analysis, 45.0%; 95.2% CI, 14.2 to 65.3;  $p = 0.007$ ) and a first episode of vaccine-type IPD was documented in 7 participants in the PCV13 group and 28 in the placebo group (vaccine efficacy in the per-protocol analysis, 75.0%; 95% CI, 41.4 to 90.8;  $p < 0.001$ ).

- 18.7. The Committee noted that analysis of pre-specified exploratory endpoints found that in all episodes of vaccine-type CAP there were 53 cases in the PCV13 group and 92 in the placebo group (vaccine efficacy in the pre-protocol analysis, 42.4%; 95% CI, 18.4 to 59.7;  $p=0.004$ ). Analysis of the first episode of confirmed pneumococcal CAP (all serotypes) found 100 cases in the PCV13 group and 144 in the placebo group (vaccine efficacy in the per-protocol analysis, 30.6%; 95.2% CI, 9.8 to 46.7;  $p=0.008$ ). The first episode of non-bacterial non-invasive CAP (all serotypes) and the first episode of all cause CAP were not significant between the two groups. The vaccine was not shown to have significant efficacy for the prevention of death from any cause. The number of deaths associated with pneumococcal disease during this study was too small to permit a meaningful analysis of the effect of the vaccine.
- 18.8. The Committee noted that the sponsor had developed a serotype-specific urinary antigen detection assay with high sensitivity and specificity for the 13 polysaccharide antigens in PCV13, in order to detect cases of vaccine-type non-bacteraemic/non-invasive CAP. The Committee raised concerns regarding the assay method. There was no evidence that it had been scrutinised or replicated outside of the study and considered that it may have underestimated other serotype antigens outside the 13 serotypes contained in Prevenar 13. The Committee discussed the possibility that the vaccine may change the ability to excrete the antigen in the urine and noted there was no consideration given to this possibility.
- 18.9. The Committee noted the safety objective was an evaluation of the safety profile of PCV13 as measured by the incidence rates of serious adverse events for 28 days after vaccination and for 6 months after vaccination among participants in the safety subgroup. Additional safety objectives were evaluations of the frequency of local reactions, systemic events, and adverse events among participants in the safety subgroup and an assessment of the number of deaths from any cause. The frequencies of pre-specified local reactions and systemic events reported in the safety subgroup were higher in the PCV13 group than in placebo and most were mild or moderate in severity. There was no significant difference between the two groups in the frequencies of newly diagnosed chronic medical conditions, serious adverse events, or deaths.
- 18.10. The Committee noted that the sponsor had included summaries of fourteen immunogenicity studies conducted between February 2007 and January 2013. These studies consistently showed that PCV 13 was non-inferior to pneumococcal polysaccharide 23 vaccine for the 12 serotypes in common. PCV13 was statistically significantly more immunogenic for the majority of common serotypes in adults aged 50-59 years compared with adults aged 60-64 years. Concomitant administration of influenza vaccine and PCV13 does not lead to biologically significant reductions in immune response to either vaccine.
- 18.11. The Committee considered the evidence was of moderate quality demonstrating a reduction in vaccine-type CAP and vaccine-type IPD but no effect on all cause of CAP and death. The Committee considered that the CAPITA data indicates that in a Dutch population, the serotype distribution in the elderly is too wide for PCV13 to have a significant effect on the incidence of all cause CAP and death for all elderly. The Committee questioned whether the incidence of CAP and IPD were same or similar between the Dutch population and New Zealanders and noted that the supplier had not included relevant New Zealand data in the application. The Committee noted that the rates of IPD for Pacific and Māori ethnic groups were approximately 4 times and 3 times higher respectively than that of the European or Other ethnic Groups.
- 18.12. The Committee considered that the sponsors cost utility analysis included costs for procedures that would not routinely be required in the general practice setting for CAP including the costs of chest x-ray, laboratory investigations and microbiological testing. The diagnosis of CAP in a NZ primary care setting is a clinical one (<http://www.bpac.org.nz/BPJ/2012/August/pneumonia.aspx>). The Committee

considered that the most important disease we would want to prevent in the over 65 population is CAP. In the CAPiTA study, only 20 to 25 % of CAP was caused by pneumococcal disease and no New Zealand data was provided to suggest the situation would be any different in New Zealand. The Committee considered that there was insufficient clinical evidence at this time to recommend universal vaccination of the population over the age of 65 years with PCV13 and that the data on PCV13 was too premature to determine whether it would be a more suitable vaccine than PPV23 in this setting.

## **19. Lidocaine 4% with adrenaline 0.1% and tetracaine 0.5% solution (Topicaine) for wound repair**

### **Application**

19.1. The Committee considered a paper from PHARMAC staff considering the funding of lidocaine 4% with adrenaline 0.1% and tetracaine 0.5% solution (Topicaine), in Section B of the Pharmaceutical Schedule, for wound repair. The Committee noted that this paper was provided in response to its request for a full review of the evidence for use in the relevant treatment settings.

### **Recommendation**

19.2. The Committee **recommended** that Topicaine be listed in Section B of the Pharmaceutical Schedule available only on a practitioners supply order (PSO), restricted to children, with a medium priority.

19.3. The Committee **recommended** that Topicaine be listed in Section B of the Pharmaceutical Schedule available only on a practitioners supply order (PSO), unrestricted, with a low priority.

19.4. 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.*

### **Discussion**

19.5. The Committee noted that Topicaine is a sterile topical solution supplied in a 5 ml syringe containing tetracaine and lidocaine, local anaesthetics, and adrenaline, a sympathomimetic for vasoconstriction. The Committee noted that the combination takes approximately 30 minutes to work and the effect lasts for about 4-6 hours.

19.6. The Committee noted that Topicaine was currently listed on the Hospital Medicines List without restrictions and is commonly used in hospital emergency departments.

19.7. The Committee noted the results of a Cochrane review published by Eidelman et al. (Cochrane Database Syst Rev. 2011 Jun 15;6:CD005364). The Committee considered that this review was dominated by topical anaesthetics containing cocaine, with only four randomised controlled trials (RCT) comparing cocaine-free topical anaesthetic with infiltrated local anaesthetic, one comparing lidocaine with adrenaline and tetracaine (LAT) solution with infiltrated local anaesthetic (Ernst et al (West J Med. 1997; 167:79-81)) and one comparing topical lidocaine-adrenaline with infiltrated local anaesthetic (Gaufberg et al (Am J Emerg Med. 2007; 25:379-84)). The Committee considered quantitative comparative analysis of data was only possible for pain scores using the visual analogue scale (VAS). The Committee noted the authors reported that, based on mostly descriptive analysis, topical anaesthetics are possibly an efficacious, non-invasive means of providing analgesia prior to suturing of dermal lacerations. The Committee noted that no serious adverse events were reported and considered that topical anaesthetics were generally well tolerated.

- 19.8. The Committee considered the results of an unblinded randomised prospective comparison trial conducted in an urban emergency department (Ernst et al. *West J Med.* 1997;167:79-81). A total of 66 adult patients with simple lacerations were allocated to either receive LAT solution or infiltrated local anaesthetic. A 10 cm VAS was used to demonstrate the pain of application, injection and suturing. Injection was reported to be significantly more painful than application of solution according to both patients and physicians. Injection median VAS 1.2 cm (IQR 0.15-2.75) versus solution median VAS 0 (IQR 0-0.15) ( $p=0.001$ ). The Committee noted that the authors considered 1.2 cm to be the minimum clinically significant difference in VAS scores. The Committee noted that anaesthesia effectiveness was not reported to be significantly different between the two treatments. The Committee considered that topical application is less painful than injected lidocaine and may reduce tissue distortion from infiltration, which may assist with wound repair. The Committee considered that Topicaine would, however, not always prevent the need for subsequent lidocaine infiltration.
- 19.9. The Committee considered the results of an unblinded RCT conducted in a hospital emergency department (Gaufberg et al. *Am J Emerg Med.* 2007;25:379-84). A total of 100 adult patients were allocated to receive either topical lignocaine-adrenaline or lidocaine with adrenaline infiltrated local anaesthetic. Pain of application on a 10 point VAS and pain during wound repair were the primary outcomes. During application patients in the injection group reported significantly more pain (42% reported VAS scores of 5 or greater) with the difference between the means of 3.98 (95%CI 3.36-4.60,  $p<0.001$ ). The Committee noted the authors reported that anaesthesia effectiveness was not significantly different between the two treatments.
- 19.10. The Committee reviewed a prospective double-blind RCT conducted in an Australian paediatric emergency department (Priestley et al. *Ann Emerg Med.* 2003;42:34-40). The Committee noted that authors reported that the application of lidocaine, adrenaline (epinephrine) and amethocaine (tetracaine) at triage reduced the total treatment time, versus placebo, in children with minor lacerations.
- 19.11. The Committee considered a study by Harman et al. (*CMAJ.* 2013;185: 629-34) that reported complete haemostasis of the wound was more common among patients who received LAT than among those who received placebo (78.2% v. 59.3%,  $p=0.008$ ). The Committee considered effective haemostasis enables more effective wound closure when suturing, enables adhesive wound closure strips to stick properly and may enable glue to bond more effectively. The Committee considered topical anaesthetics containing adrenaline are likely to provide faster haemostasis than no treatment, although likely to be slower and less effective than infiltrated local anaesthetic at providing anaesthesia to the wound.
- 19.12. The Committee considered a randomised double-blind clinical trial investigating lidocaine, adrenaline (epinephrine), tetracaine (LET) versus lidocaine and prilocaine (EMLA) for pre-treating lacerations (Singer & Stark *Acad Emerg Med.* 2001;8:223-30). The Committee noted similar efficacy was reported for both agents, however, it considered that EMLA was not approved for use on non-intact skin and does not contain adrenaline which assists with haemostasis.
- 19.13. Overall, the Committee considered that the evidence for Topicaine is comprised of small RCTs of moderate to poor quality, on adults and children with minor lacerations, demonstrating similar anaesthetic efficacy as infiltrated local anaesthetic using lidocaine, less pain on application than infiltrated lidocaine, but with a slower onset of action.
- 19.14. The Committee considered that there were no trials comparing topical anaesthetics to inhalational agents, and if available, that these agents would be likely to be used as well as topical or injected local anaesthetic rather than instead of.

- 19.15. The Committee noted that Topicaine takes approximately 30 minutes to take full effect and considered that this may limit the usefulness of Topicaine, unless it was applied by a triage nurse prior to consultation with the physician. The Committee considered that if Topicaine was funded, it would need to be available on a Practitioners Supply Order (PSO) to enable access in clinic when needed. The Committee considered that tissue glue is often used to repair wounds and that this is relatively fast to apply but in children frequently causes burning pain due to an exothermic reaction. The Committee considered that if Topicaine was funded, children who have lacerations repaired with glue would be likely to routinely have Topicaine applied beforehand, whereas currently they may have no local anaesthetic prior to application of glue.
- 19.16. The Committee considered that, if Topicaine was funded, there may be a slight reduction in the use of lignocaine 1% injection, due to a theoretical reduction in the need for lidocaine infiltration.
- 19.17. The Committee considered that Topicaine would be used primarily for local anaesthesia when repairing or cleaning traumatic wounds, and that PHARMAC's estimates for patient numbers appeared to be reasonable. The Committee considered, however, if Topicaine was funded, that there could be considerable use in areas other than wound repair, such as chronic ulcer debridement and chronic wound management. The Committee considered there was no available evidence to support the use for chronic ulcer debridement and chronic wound management, and that it would be difficult to target use sufficiently to avoid this.
- 19.18. The Committee considered that preventing procedural pain is a high priority in paediatric emergency care. The Committee considered that inadequate analgesia for this patient group can result in more complicated procedures, use of sedation, increased pain sensitivity for future procedures and lengthened treatment time.
- 19.19. The Committee considered that children with minor lacerations would be the patient population most likely to benefit from Topicaine; as pain from injections may cause significant agitation and distress which may affect treatment outcomes. The Committee considered that children, unlike adults, are often unable to verbalise their level of pain and it is preferable to avoid the need for physical restraints or sedation where possible. Members considered that if a child experiences pain and anxiety, wound repair may have to be abandoned in community settings and children may need to be referred to an emergency department. The Committee considered that the use of Topicaine may increase the success rate of wound repair for children in community settings which, theoretically, could help reduce the number of referrals to emergency departments.

## **20. Sodium chloride prefilled syringe (PosiFlush XS) for sterile procedures**

### **Application**

- 20.1. The Committee considered a funding application from Becton, Dickinson and Company (BD) for the listing of Sodium chloride externally sterile prefilled syringe (PosiFlush XS) in part II of Section H of the Pharmaceutical Schedule for flushing of an in-situ vascular access device when used in a sterile field using aseptic techniques.

### **Recommendation**

- 20.2. The Committee **recommended** that PosiFlush XS be listed in part II of Section H of the Pharmaceutical Schedule for use in flushing of in-situ vascular access devices only when used in a hospital sterile field environment using sterile gloves and aseptic techniques, with a high priority.
- 20.3. 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; (v)*

*The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

## **Discussion**

- 20.4. The Committee noted the product being considered in this funding application is similar to BD Posiflush SP currently listed in part II of Section H of the Pharmaceutical Schedule, except that the product is externally sterile. BD Posiflush SP is currently restricted to use for flushing of in-situ vascular access devices only.
- 20.5. The Committee noted that PosiFlush XS would likely be used in high-risk environments where current aseptic technique involves two people, one inside the sterile field with a sterile syringe and needle drawing up saline from an ampoule being held by the other person outside the sterile field. The Committee considered that use of PosiFlush XS is likely to reduce the staff time required for a procedure when compared to this alternative method.
- 20.6. The Committee noted feedback forms from New Zealand based clinicians provided by the supplier as part of the application. The feedback received was positive and included recurring themes such as time-savings, reduced risks of contamination, good labelling and the reinforcement of best practice.
- 20.7. The Committee noted a retrospective cohort study by Bertoglio et al. (J Hosp Infect. 2013;84:85-8) comparing the incidence of catheter related bloodstream infections (CRBSI) when either pre-filled or manually filled syringes are used for the flushing of totally implantable venous access devices. The Committee considered that this study provides evidence of low quality for the reduction in infections using prefilled syringes, although its relevance to PosiFlush XS is limited. The study has a number of significant inherent limitations including a lack of randomisation, the absence of a sterile field for procedures and differences in procedure timing allowing other factors including education to potentially influence the results.
- 20.8. The Committee noted an observational study by Keogh et al. (J Infus Nurs. 2014 ;3:96-101) demonstrating reduced clinician handling and an average time-saving of 49 seconds for prefilled syringes versus manually filling syringes. The Committee questioned whether these same time savings would be possible in normal clinical practice situations. The Committee noted the observation of poor compliance with aseptic techniques during the study.
- 20.9. The Committee noted a letter to the editor by Worthington et al. (The Hospital Infection Society, letters to the editor. 2001) detailing an observational study comparing prefilled saline syringes with manual filling. No microbes were present in the saline of any of the prefilled syringes, whereas 2% of the manually filled syringes were contaminated. The Committee considered this study provides some low quality evidence for the use of prefilled over manually filled syringes. The study failed to demonstrate any added advantage of externally sterile syringes, as no differences in contamination between internally sterile and externally sterile syringes were detected. The Committee noted that the administration was not performed in a sterile field and there was a general observation of poor compliance with aseptic techniques during the study.
- 20.10. The Committee noted there is no published clinical evidence specifically supporting the use of externally sterile prefilled syringes such as PosiFlush XS, although there is some weak and low quality evidence for the use of prefilled syringes over manually filled syringes.
- 20.11. The Committee concluded that based on a first principles approach, there is likely validity in the concept that externally sterile prefilled syringes would be associated with less catheter related bloodstream infections compared to of drawing up from a non-sterile ampoule, but only when used in an environment with a sterile field by clinicians

using sterile gloves and appropriate aseptic techniques. Environments with a sterile field could include, but may not be limited to, operating theatres, catheter laboratories, some oncology wards and intensive care units. The Committee agreed that clinician time-savings are likely and would be of additional benefit.

- 20.12. The Committee agreed that externally sterile prefilled syringes are unlikely to provide any additional benefits over current no touch aseptic techniques in community situations without an established sterile field.
- 20.13. The Committee recommended PHARMAC seek further specialist advice from The Infection Prevention & Control Nurses College (IPCNC) regarding the clinical significance of externally sterile prefilled saline syringes.