

PTAC meeting held on 7 & 8 February 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. Matters Arising / Correspondence

Diabetes Management

- 1.1. The Committee noted receipt of the positive correspondence received from three clinicians in relation to funding for the anti-diabetic agents including GLP-1 agonists, DPP4-inhibitors-4 and SGLT-2 inhibitors.

Pertuzumab

- 1.2. The Committee noted correspondence from Roche Products (New Zealand) Limited regarding pertuzumab (Perjeta) for the first-line treatment of patients with HER2 – positive metastatic breast cancer. Members noted that Roche had provided information from a final overall survival analysis from the pivotal phase III study (CLEOPATRA) including a slide show of a presentation from the European Society of Medical Oncology Meeting held on 28 September 2014. The Committee noted that at its November 2014 meeting it had reviewed correspondence from the Breast Cancer Aotearoa Coalition (BCAC) that included an abstract of this presentation. The Committee reiterated its November 2014 recommendation that it review the final overall survival analysis from the CLEOPATRA study once it was published and an updated cost effectiveness analysis had been undertaken.

Ferric Carboxymaltose

- 1.3. The Committee noted correspondence from Vifor regarding proposed Special Authority criteria for a community listing of ferric carboxymaltose in August 2014. Members noted the Haematology Subcommittee reviewed this correspondence at its October 2014 meeting and Vifor submitted further correspondence in response to the Haematology Subcommittee minutes.
- 1.4. The Committee noted that PHARMAC listed ferric carboxymaltose in Section H of the Pharmaceutical Schedule in August 2014 and PHARMAC intends to develop a proposal to list it in Section B. The Committee noted the significant budget impact and fiscal risk of listing of ferric carboxymaltose in Section B and considered it is very difficult to develop Special Authority criteria that would minimise this risk. Members noted progressing with a community listing would shift the cost of iron infusion from the hospital setting to the Community Pharmaceutical Budget. The Committee noted PHARMAC are continuing to engage with stakeholders regarding provision of infusion services in the community.
- 1.5. The Committee considered that patient compliance with oral treatment should also be included in the proposed criteria. The Committee noted restricting use to any Specialist would enable a vocationally registered general practitioner (GP) to prescribe ferric carboxymaltose for patients with a serum ferritin ≤ 20 mcg/L, however considered this may disadvantage some communities with no vocationally registered GP and limit access. The Committee **recommended** the prescriber should be amended to allow any relevant practitioner to prescribe for this group. Members noted this would have minimal impact on patient numbers as use would be substantial either way. The Committee agreed with the Haematology Subcommittee recommendation that a specialist should be consulted prior to treatment in patients with a ferritin level of > 20 mcg/L.
- 1.6. The Committee **recommended** that ferric carboxymaltose is listed in Section B of the Pharmaceutical Schedule subject to the following Special Authority restriction:
Initial application – (serum ferritin ≤ 20 mcg/L) from any relevant practitioner. Approval valid for 3 months for applications meeting the following criteria:
Both:
 1. Patient has been diagnosed with iron-deficiency anaemia with a serum ferritin level of ≤ 20 mcg/L; and

2. Any of the following:
 - 2.1. Patient has been compliant with oral iron treatment and treatment has proven ineffective;
 - 2.2. Treatment with oral iron has resulted in dose-limiting intolerance; or
 - 2.3. Rapid correction of anaemia is required.

Initial application – (serum ferritin >20 mcg/L) only from an internal medicine specialist, obstetrician, gynaecologist or anaesthetist or any other Specialist on recommendation of an internal medicine specialist, obstetrician, gynaecologist or anaesthetist. Approval valid for 3 months for applications meeting the following criteria:

Both:

1. Patient has iron-deficiency anaemia with a serum ferritin level of > 20 mcg/L; and
2. Any of the following:
 - 2.1. Patient has been compliant with oral iron treatment and treatment has proven ineffective;
 - 2.2. Treatment with oral iron has resulted in dose-limiting intolerance; or
 - 2.3. Rapid correction of anaemia is required.

Renewal – (serum ferritin ≤ 20 mcg/L) from any relevant practitioner. Approval valid for 3 months for applications meeting the following criteria:

1. Patient continues to have iron-deficiency anaemia with a serum ferritin level of ≤ 20 mcg/L; and
2. A re-trial with oral iron is clinically inappropriate.

Renewal – (serum ferritin >20 mcg/L) only from an internal medicine specialist, obstetrician, gynaecologist or anaesthetist or Specialist on recommendation of an internal medicine specialist, obstetrician, gynaecologist or anaesthetist. Approval valid for 3 months for applications meeting the following criteria:

Both:

1. Patient continues to have iron-deficiency anaemia with a serum ferritin level of > 20 mcg/L; and
2. A re-trial with oral iron is clinically inappropriate.

2. Subcommittee Minutes

Analgesic Subcommittee

- 2.1. Regarding paragraph 5.2 the Committee noted that the Subcommittee recommended that the availability of funded tramadol oral liquid 10 mg/ml be communicated to the Australian and New Zealand College of Anaesthetists (ANZCA), the Australian and New Zealand Society of Palliative Medicines (ANZSPM), the Paediatric Society of New Zealand, NZ Formulary and relevant hospital staff. The Committee recommended that this is also communicated to the Pharmaceutical Society of New Zealand.
- 2.2. Regarding paragraphs 5.13 and 5.14 the Committee agreed with the suggested changes to the Special Authority criteria for aprepitant for the prevention of PONV and considered that these changes would further target treatment to those who are most likely to benefit. The Committee did not agree with the recommendation from the Subcommittee to change the priority rating for aprepitant for PONV. The Committee considered this application should remain a low priority for funding but would be willing to review the priority should new evidence become available to support the efficacy of aprepitant in the prevention of PONV for the population targeted by the Special Authority criteria.
- 2.3. The Committee noted and accepted the remainder of the record of the meeting.

Haematology Subcommittee

- 2.4. The Committee noted and accepted the Subcommittee's recommendation to update the PHARMAC dabigatran guidelines. The Committee also noted that in Australia, some hospitals have started routinely monitoring the therapeutic effect of dabigatran following

the publishing of the Cohen D British Medical Journal article (*BMJ* 2014; 349: g4670). Unlike with warfarin, this monitoring is only done for short period of time at the beginning of dabigatran therapy because drug-food interactions are not as significant a concern with dabigatran.

2.5. The Committee noted and accepted the remainder of the record of the meeting.

Immunisation Subcommittee

2.6. With the exception of item 4.11, the Committee noted and accepted the minutes from the Immunisation Subcommittee held on the 3 September 2014.

2.7. The Committee did not accept the recommendation in item 4.11 to widen the access to Hepatitis A vaccine to include patients living with HIV. The Committee considered that the majority of people living with HIV were not at any greater risk of contracting hepatitis A than the general public. The Committee considered that there were three subsets of patients living with HIV who were at greater risk either of contracting hepatitis A or greater morbidity having contracted the disease. The three subsets are men having sex with men, those with chronic renal failure and IV drug users. The Committee recommended the reference to HIV be amended to specify these three groups.

Rare Disorders Subcommittee

2.8. The Committee noted the record of the meeting of the Rare Disorders Subcommittee on 5 November 2014 and accepted the recommendation in paragraph 3.2.

Rheumatology Subcommittee

2.9. The Committee noted the record of the meeting of the Rheumatology Subcommittee on 7 October 2014.

2.10. The Committee accepted the recommendations in paragraphs 4.2, 5.24 and 5.27.

2.11. Discussions in relation to the recommendations in paragraphs 6.18 and 6.19 were deferred until the broader discussion of febuxostat and benzbromarone later in the meeting.

2.12. Discussions in relation to the recommendations in paragraphs 7.13 and 8.7 were deferred until the broader discussions of tumour necrosis factor (TNF)-alpha inhibitors for spondyloarthropathies later in the meeting.

Ophthalmology Subcommittee

2.13. The Committee noted and accepted the recommendations of the Ophthalmology Subcommittee meeting held on 30 October 2014 regarding biosimilar infliximab.

2.14. The Committee noted the recommendations of the Subcommittee regarding aflibercept for wet age-related macular degeneration and noted that this funding application will be discussed further at this meeting.

2.15. The Committee noted that the remainder of the minutes will be reviewed at the next PTAC meeting in May 2015.

3. Tocilizumab for idiopathic multicentric Castleman's disease

Application

3.1. The Committee reviewed an application from a clinician for the funding of tocilizumab (Actemra) for the treatment of HHV-8 negative idiopathic multicentric Castleman's disease (iMCD).

Recommendation

- 3.2. The Committee **recommended** that access to tocilizumab is widened to include HIV/HHV-8 negative idiopathic multicentric Castleman's disease in Section H of the Pharmaceutical Schedule with a low priority subject to the following restrictions:

Initiation – idiopathic multicentric Castleman's disease

Haematologist or rheumatologist

Re-assessment required after 6 months

All of the following:

- 1 Patient has severe HIV/HHV-8 negative idiopathic multicentric Castleman's disease; and
- 2 Treatment with at least 6 months of corticosteroids is ineffective; and
- 3 Treatment with chemotherapy is clinically inappropriate; and
- 4 Tocilizumab to be administered at doses no greater than 8 mg/kg IV every 4 weeks.

Continuation – idiopathic multicentric Castleman's disease

Haematologist or rheumatologist

Re-assessment required after 6 months

The patient has a sustained improvement in inflammatory markers and functional status.

- 3.3. The Committee also noted siltuximab is undergoing registration in New Zealand and recommended that it should also be assessed by the Committee for this indication.
- 3.4. The Committee **recommended** that PHARMAC seek further details regarding the application of tocilizumab for AA amyloidosis.
- 3.5. 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; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 3.6. The Committee noted tocilizumab is an anti-IL-6 monoclonal antibody and interleukin-6 (IL-6) plays a central role in the pathophysiology of MCD. Members noted MCD is associated with HIV and HHV-infection, however there is also a group of people with HIV-negative and HHV-8 negative MCD with unknown aetiology and pathophysiology often referred to as idiopathic MCD (iMCD). The Committee noted tocilizumab is registered for use in iMCD in Japan and India, however it is an off-label indication in New Zealand. The Committee noted that registration for this indication in New Zealand is unlikely due to the lack of randomised controlled trials.
- 3.7. The Committee considered the evidence available to be of weak to moderate strength and low quality, limited to small open-label studies and case reports. Members noted the key difficulty with the data is the lack of an agreed primary end-point or disease index; therefore many authors have used surrogate end points such as response to C-reactive protein (CRP) and haemoglobin (Hb).
- 3.8. The Committee noted an open-label, prospective cohort study of tocilizumab in 28 patients with iMCD (Nishimoto et al, Blood 2005;106(8):2627). Members noted participants (median age 38 years, median disease duration 4 years) mainly had organomegaly and lymphocytic interstitial pneumonia and these patients represent mild/moderate disease rather than severe disease. Fifteen patients were receiving corticosteroids, and only 4 patients had received chemotherapy with other agents. Patients received 8 mg/kg tocilizumab intravenously every 2 weeks for 16 weeks,

followed by tailored individualised dosing. The primary efficacy end-point was disease activity as measured by Hb, CRP, albumin, and a visual analogue scale (VAS) fatigue rating. Secondary end-points included changes in lymph node size and serum amyloid A protein (SAA). At Week 6, patients treated with tocilizumab had significant improvements in CRP, fibrinogen, SAA, and ESR from baseline ($p < 0.001$). At week 16, CRP had returned to normal levels in 18 (64%) and fatigue scores ($p = 0.01$), albumin and IgG values were also improved ($p < 0.001$; week 16 vs. baseline). Patients who had anaemia at baseline (mean Hb 92 g/L) experienced improvement after tocilizumab treatment (Hb increased to 120 g/L, SD=21) at week 16. Lymph nodes had decreased to < 10 mm in 10 (43%) of 23 patients after 16 weeks of treatment and in 12 (52%) of 23 patients after 1 year. The median duration of tocilizumab treatment was 65 weeks (range 55-76 weeks). Adverse reactions were common, but transient and spontaneously resolved.

- 3.9. The Committee also noted a retrospective report on 13 patients from New Zealand (Zhai and Simpson, ASH abstract 2013 from the 55th Annual Meeting). Twelve patients were HIV/HHV8 negative (median age at diagnosis of 53 years), of whom 10 were Polynesian. Members noted Polynesian subjects had fewer general symptoms compared to the literature: weight loss 40%, fever 20%, skin lesions 60%, splenomegaly 60% and polyarthralgia related to MCD 40%. Median baseline CRP and Hb was 105 mg/L (39-219) and 89 g/L respectively. Previous therapies included corticosteroid (dexamethasone or prednisone), rituximab and chemotherapeutic agents with mixed but mostly non-durable response until 2009. From this time those needing treatment were given tocilizumab (6) or siltuximab (2). Tocilizumab was administered at 8 mg/kg as an IV infusion in 3-4 weekly cycles. Members noted CRP was used to measure response to treatment aiming for a low CRP (< 20 mg/L) at the end of each cycle, and used to achieve increasing treatment intervals. The median duration of therapy was 19 months with normalisation of Hb in all 6 patients (median Hb 87 g/L (69 - 140) increasing to 133 g/L (118 - 157)) and improvement in CRP (median CRP 86 mg/L (39 - 160) improved to 4 mg/L (1 - 23)). Treatment was stopped in two of the six patients with subsequent relapse, and response to tocilizumab retreatment. Members noted there were three deaths in the entire patient group and these were before IL-6 specific therapy was available.
- 3.10. The Committee noted the reports on the use of tocilizumab in children for MCD is very limited. Kozlova et al (European League Against Rheumatism Abstract 2013, Madrid) report use in 3 children without good efficacy who all required further escalation in treatment, while Galeotti et al (Mol Cancer Ther 2012;11:1623-6) report a sustained response in 2 children.
- 3.11. The Committee considered rituximab (an anti-CD20 monoclonal antibody) may be an alternative treatment to anti-IL-6 agents in iMCD. Members noted PHARMAC has previously approved two NPPA applications for rituximab in iMCD. Members noted evidence of rituximab for iMCD is limited to case reports. Ocio et al (Am J Hematology 2005;78:302-52005) report complete remission following eight courses of rituximab in a 23 year old with HIV/HHV-8 negative disease and extensive abdominal involvement and haemolytic anaemia. Ide et al (Eur J Haematol 2006;76:119-23) report near complete remission in two out of three patients.
- 3.12. The Committee noted other treatment options for iMCD include corticosteroids, chemotherapeutic agents usually in combination such as cyclophosphamide, doxorubicin, vincristine and prednisone. Members noted a single case report of using cyclosporin for this indication.
- 3.13. The Committee noted siltuximab is another monoclonal antibody with high affinity to IL-6 and has FDA and EMA approval for the treatment of MCD who are HIV/HHV-8 negative. Members noted siltuximab is currently undergoing registration assessment with Medsafe. The Committee noted siltuximab is the only agent with randomised controlled trial data for HIV/HHV-8 negative MCD. A multicentre, randomised, double-blind, phase

II trial of siltuximab in 79 patients with symptomatic HIV/HHV-8 negative MCD demonstrated significant benefit of siltuximab for all end points when compared to placebo (Lancet Oncol. 2014;15(9):966-74). Siltuximab 11 mg/kg IV every three weeks resulted in an overall response rate of 34% compared with 0% and a longer median time to treatment failure. Improvements in anaemia and markers of inflammation were also seen. The Committee considered that the quality of evidence for siltuximab appeared better than for tocilizumab, and that siltuximab may be preferable to tocilizumab if it gained Medsafe registration and was available in New Zealand. However, the Committee would need to assess a funding application for this agent before making any recommendations regarding its use.

- 3.14. The Committee noted the incidence of HHV-8 negative MCD is estimated to be 2 per million, however there is a higher incidence in Polynesian people (Samoan, Māori, Niuean, Tongan) and this contributes to the higher rates seen in New Zealand with a reported point prevalence of 5 per million in 2013 (Heyland et al; International Society of Haematology Abstract 2014). Members considered this is consistent with rates in Melbourne and Hong Kong. Members noted there may be reasonable number of undiagnosed patients. The Committee considered an estimate of 40 patients in New Zealand with HHV-8 negative MCD would be appropriate.
- 3.15. The Committee considered a 4-weekly dosing regimen of tocilizumab would be appropriate and this should be used for cost-effectiveness analysis. The Committee noted there is currently no evidence available to suggest there is any difference between tocilizumab and comparators in survival benefit or rates of hospital admissions. Members noted use of chemotherapy may increase hospitalisations to manage adverse events.
- 3.16. The Committee noted patients with iMCD have a poor quality of life and high health need with increased risk of infection and lymphoma. Members considered patients with iMCD may have a greater disease burden compared to other autoimmune conditions.
- 3.17. The Committee noted the application also included information regarding the use of tocilizumab for AA amyloidosis. Members considered PHARMAC should request further information regarding this indication and patient group prior to the Committee reviewing it further.

4. Varicella Vaccine

Application

- 4.1. The Committee reviewed further information on varicella vaccination.

Recommendation

- 4.2. The Committee **recommended** varicella vaccine be funded with a high priority as a part of a universal childhood immunisation. It is noted that one member of the Committee abstained from voting.

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.*

Discussion

- 4.3. The Committee noted that at its March 2013 meeting the Immunisation Subcommittee had recommended funding universal childhood varicella vaccination with a high priority, recommending that one dose be given at 15 months with a catch up programme at age 12-13 years. The Committee noted that PTAC reviewed the application at its August 2013 meeting and recommended declining a universal childhood varicella vaccination program until further information was available regarding the long term durability of the vaccination and the incidence of varicella and herpes zoster in the wider population following the introduction of universal childhood varicella vaccination. The Committee did recommend funding varicella vaccination to prevent transmission to high risk individuals with a high priority.
- 4.4. The Committee reviewed three analyses of the incidence of varicella in New Zealand – a commentary (Walls T, Wilson E: Has the time come for universal varicella (chickenpox) vaccination in New Zealand. *NZ Med J* 2010;123:22-4), active surveillance of cases nationwide ((poster) Wen et al. Prospective Surveillance of Hospitalisations Associated with Varicella-Zoster Virus Infections in New Zealand Children), and a retrospective audit (Wen et al. Varicella in a Paediatric Intensive Care Unit: 10-year review from Starship Children’s Hospital, New Zealand. *J. Paediatr. Child Health* 2014 April;50(4):280-5).
- 4.5. Wen et al (poster) reported a hospitalisation rate of 8.3/100,000 children per year, with Māori and Pacific Island children being over-represented (40% of hospitalisations being Māori, 34% New Zealand European and 22% Pacific Island). They reported that 75% of the children had infective complications (predominantly *Staphylococcus aureus* & *Streptococcus pyogenes*). Smaller numbers of children had neurological complications (stroke, ataxia, encephalitis & febrile convulsions). The Committee noted that New Zealand’s Staphylococcal and Streptococcal skin infection hospital admission rates are higher than any other western country and that the burden of disease and the secondary skin infections are disproportionately high amongst Māori and Pacific Island children. The Committee noted that the papers from Walls and Wen may under-estimate the actual incidence and hospitalisation rates as they rely on centres reporting to the New Zealand Paediatric Surveillance Unit and while a few centres are vigilant about reporting many others under-report.
- 4.6. In the 2014 study by Wen et al, the Committee noted that of the 26 cases reviewed, 85% were Māori or Pacific Island, four patients died (three of whom were immunocompromised) and a further 8 (23%) had ongoing disability at discharge from hospital.
- 4.7. The Committee noted the Systematic Review of evidence on the effectiveness and duration of protection of varicella vaccines prepared for the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) meeting in April 2014. Forty of the studies included in the review assessed vaccine effectiveness and 31 articles were reviewed in the assessment of waning immunity of varicella vaccines. The review reported that a single dose of Varicella vaccine appears to be moderately effective (approximately 80%) for preventing varicella of any severity; highly effective (~ 95%) for preventing moderate to severe disease and very highly effective (~99%) for preventing severe disease only.
- 4.8. The Committee noted three studies reporting on changes in the epidemiology of varicella and/or Herpes zoster following the introduction of universal varicella vaccination. A retrospective study in the US by Hales et al (Examination of links between herpes zoster incidence and childhood varicella vaccination. *Ann Intern Med* 2013;159:739-45) obtained health care claims data for 2.8 million Medicare beneficiaries older than 65 years from 1992 to 2010, with a median follow-up of 7 years. They reported the incidence of age and sex standardised herpes zoster incidence increased 39% from 10.0 per 1000 person years in 1992 to 13.9 per 1000 person years in 2010. Mean age at the time of herpes zoster diagnosis remained stable at 76.9 years in 1999 and 77.9 years in 2010. They reported that the exponentiated parameter estimate for the

interaction between calendar year and the indicator variable for the early varicella vaccine implementation period was 1.002 (95% CI, 0.984 to 1.020), indicating that the annual increase in herpes zoster incidence during this period (1996 to 1999) was 0.2% higher than that during the pre-implementation period (1992 to 1995) but this faster increase was not statistically significant. Similarly the exponentiated parameter estimate for the interaction between calendar year and the indicator variable for the full varicella vaccine implementation period (2000-2010) was 1.008 (95% CI, 0.994 to 1.023).

- 4.9. The slope of the increase in herpes zoster incidence over the period studied did not change after varicella vaccine was introduced in 1996. No correlation was found between state-wide vaccination compliance and herpes zoster incidence.
- 4.10. Baxter et al (Impact of Vaccination on the Epidemiology of Varicella:1995-2009. *Paediatrics* 2014;134:24-30) conducted five cross-sectional surveys during 1994-95 (pre vaccination), 2000, 2003, 2006 and 2009 in Northern California. Between 8,400 to 8,900 participants were surveyed each time. They reported that the proportion of unvaccinated children reporting ever having varicella decreased from 84.6% in 1995 to 37.9% in 2009 and that varicella incidence rates declined significantly across all age groups by 91-96% between 1995 and 2009. Hospitalisations with a primary diagnosis of varicella decreased 13% annually between 1994 and 2006 (incidence rate ratio 0.87, CI 0.84-0.90 p<0.001). The authors concluded that varicella vaccination protects both directly and through herd immunity.
- 4.11. Heywood et al (Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study. *Bull World Health Org.* 2014;92:593-604) examined the trends in varicella and herpes zoster hospitalisations following the availability and funding of single dose varicella vaccination in Australia. The committee noted that 60% of varicella hospitalisations over the study period were attributed to Aboriginal or Torres Strait Island children. The authors reported that in the 0 to 4 years age group the hospitalisation rate in indigenous children, which was double that of non-indigenous children (incidence rate ratio (IRR) 1.9, 95%CI 1.4-2.7), declined 3-fold, from 71.8 in the pre-vaccine period to 16.6 per 100,000 population in the immunisation programme period – becoming similar to the hospitalisation rates for non-indigenous children (IRR 1.1, 95%CI 0.7-1.6). The Committee noted that this effect may be transferable to New Zealand's Māori and Pacific Island children who are over-represented in hospitalisation rates.
- 4.12. The Committee noted that varicella vaccine could be given in combination with the HiB, MMR and pneumococcal vaccine at 15 months and that if a catch up were to be given it could be given with the diphtheria/tetanus/pertussis vaccination in year 7 (11 to 12 year olds). While some members of the Committee considered that introducing a fourth injectable vaccine at 15 months could be problematic the majority of the Committee considered that it is acceptable to give four injections at that time.
- 4.13. The Committee noted that the biggest uncertainty in introducing varicella vaccination in the paediatric population is the possible effect it may have on the incidence of zoster and/or varicella disease in the older population. The Committee noted that varicella disease in the older population is a significantly more severe disease than that experienced by the younger, <5 year-old population. In addition, zoster has a high level of morbidity in the elderly.
- 4.14. The Committee noted that no outbreaks of varicella in the older population have been seen in either the US or Australia following the introduction of universal varicella vaccination. The Committee noted that there has been a statistically significant increase in the incidence of zoster in these countries over time, but whether that increase is due to vaccination or to other factors is unclear. The Committee noted that it was not possible to determine from the evidence presented to it why there may be an increase in the incidence of zoster. The Committee also noted that there is an effective vaccine for

herpes zoster, which may be a future means for dealing with increased rates of zoster in older adults.

- 4.15. The Committee noted that most people in the US and Australian studies still had immunity to varicella from natural infection in childhood. Therefore it would not be expected that adolescent and young adult rates of varicella infection would be on the increase at this stage. As a result, the epidemiological studies discussed by the committee were recognised to have significant limitations in addressing changes in varicella age related incidence that are likely to occur twenty or thirty years after the introduction of the vaccine. The Committee considered that with non-immune individuals, outbreaks of disease are likely to occur in the adolescent, young adult and older populations. The Committee considered that the rate of varicella wild type infection would depend largely on vaccination rates, for example if the vaccination rate is 99% then there is a lower likelihood of significant outbreaks of varicella in older age groups, but if the vaccination rate is <80% then the chances are very high that there would be varicella outbreaks in older individuals with associated increased morbidity and mortality.
- 4.16. The Committee noted that New Zealand has good vaccination coverage currently at 95% (two year olds fully vaccinated) but commented that if vaccination rates are not maintained at that level, varicella rates would be likely to increase in the older age groups who would likely have more severe disease.
- 4.17. The Committee noted that varicella vaccination had had a very positive effect on the indigenous peoples in Australia and could be expected to have the same effect here in New Zealand. The Committee noted that while vaccination against varicella may result in changes in the incidence of varicella and herpes zoster in the older population in the future, the Australian and US experience had not shown this in the short to medium term. The Committee considered that while the question as to whether or not universal vaccination against varicella should be included in the National Immunisation Schedule may be complex, there is clear benefit not just to the individual but also to public health. The Committee noted that the Baxter study reported 20 years and more follow-up data and it would be difficult to get better observational data at this time. The Committee considered that if there are any future increases in the incidence of varicella disease or herpes zoster in the older populations a booster dose of varicella vaccine may be needed and/or the addition of zoster vaccination to the National Immunisation Schedule.
- 4.18. The Committee noted that different countries had evaluated the same data that PTAC was evaluating and arrived at differing viewpoints – the US and Australia have included universal mass varicella vaccination in their vaccination schedule , while the UK has not yet included varicella vaccination in its programme electing to fund zoster vaccine first. The Committee noted that the patients who are hospitalised with varicella comprise about 1% of the patients with varicella who are seen in general practice. The prevention of 430 hospitalisations by vaccination can be multiplied by up to 100 to determine the number of children GPs may see with chicken pox.
- 4.19. The Committee noted that the major benefit of vaccination with varicella vaccine may be observed in the Māori and Pacific Island paediatric population. However the Committee noted that there is no data for the child bearing age groups of 20 to 30 year olds who have no immunity and are unvaccinated. There have been no reports yet from Australia or the United States to indicate an increase in the incidence of congenital varicella syndrome since the introduction of varicella vaccination, but that it may still be too early to evaluate this given that these maternal cohorts will have immunity from infection in childhood with wild type virus.
- 4.20. Some members of the Committee considered the disease modelling may need to be reviewed to include a younger population, as half of the people who contracted herpes zoster were under the age of 65 years, so that the published modelling currently excludes half the population with herpes zoster infection.

- 4.21. The Committee noted the result of the Cost Utility Analysis and considered that the assumptions used in the model were appropriate.
- 4.22. The Committee noted that for vaccination against varicella to be effective, patients would eventually require two doses, as wild-type varicella incidence in the paediatric population decreases.
- 4.23. The Committee recommended Varicella vaccine be listed on the Pharmaceutical Schedule funded for one infant dose at age 15 months and one catch up dose at 11 or 12 years of age, with a high priority. One member abstained from voting.

5. Zoledronic Acid for use in postmenopausal early breast cancer

Application

- 5.1. The Committee reviewed an application from the New Zealand Breast Cancer Special Interest Group (NZBCSIG) for the funding of zoledronic acid (Zometa) for adjuvant use in postmenopausal women with early breast cancer.

Recommendation

- 5.2. The Committee **recommended** that the application for adjuvant zoledronic acid in postmenopausal women with early breast cancer be declined.
- 5.3. The Committee also **recommended** that the funding application be provided to the Cancer Subcommittee of PTAC (CaTSoP) for review.
- 5.4. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services.*

Discussion

- 5.5. The Committee noted that zoledronic acid 0.8 mg per ml, 5 ml vial (Zometa) is currently funded for the treatment of hypercalcaemia of malignancy, treatment of pain in patients with bone metastases and prevention of skeletal-related events in patients with bone metastases, subject to Special Authority criteria. Members noted that this application was for the funding of adjuvant zoledronic acid, given at 6 monthly intervals for 5 years, in postmenopausal women with early breast cancer to reduce the risk of breast cancer recurrence with bone metastases and to improve breast cancer survival. Members noted that this was not a currently licenced indication for zoledronic acid.
- 5.6. The Committee noted that various randomised controlled studies show that bisphosphonates, such as zoledronic acid, reduce bone pain, improve quality of life and reduce the number of, and time to, skeletal events, such as fractures, in patients with bone metastases from various cancers, including breast cancer. Members also noted that animal models suggested that bisphosphonates may also have a direct anti-tumour activity, acting through inhibiting cell migration and invasion, and inducing apoptosis in cancer cells.
- 5.7. The Committee reviewed evidence from 2 open label randomised controlled trials, ABCSG-12 (Gnant et al. Lancet Oncol. 2011;12(7):631-41; Gnant et al. Annals of Oncology 26: 313–320, 2015) and AZURE (Coleman et al. N Engl J Med. 2011;365:1396-405; Coleman et al. Lancet Oncol. 2014;15:997-1006), that were specifically designed and powered to explore breast cancer recurrence as a primary endpoint after adjuvant zoledronic acid treatment. Members noted that the primary end

point of both studies was disease free survival with secondary end points including overall survival.

- 5.8. The Committee noted that the ABCSG-12 study enrolled 1803 premenopausal women with stage I or II endocrine sensitive early breast cancer. All patients received ovarian suppression with goserelin (to render a postmenopausal status). Members noted that the study had a two-by-two factorial design comparing the efficacy and safety of anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years. Members noted that with 62 months median follow-up, zoledronic acid reduced risk of disease-free survival (DFS) events (HR 0.68, 95% CI 0.51–0.91; $p=0.009$), but did not significantly affect overall survival (OS) (30 deaths with zoledronic acid vs 43 deaths without; HR 0.67, 95% CI 0.41–1.07; $p=0.09$). Members noted that at 94.4-month median follow-up these results were maintained but with broad confidence intervals and were not significant at the predefined significance level (DFS HR 0.77; 95% CI 0.60-0.99 $p = 0.042$, OS HR= 0.66; 95% CI 0.43 – 1.02; $p= 0.064$). Members noted that absolute risk reductions with zoledronic acid were 3.4% for DFS and 2.2% for OS.
- 5.9. The Committee noted that the AZURE trial enrolled 3360 pre and postmenopausal women with stage II or III breast cancer and compared standard adjuvant chemotherapy with or without zoledronic acid (4 mg administered every 3 to 4 weeks for 6 doses and then every 3 to 6 months to complete 5 years of treatment). Members noted that 45% of the patients enrolled in the AZURE trial were premenopausal (0.2% received goserelin). Members noted that the number of DFS events did not differ between groups: 493 in the control group and 473 in the zoledronic acid group (adjusted hazard ratio [HR] 0.94, 95% CI 0.82–1.06; $p=0.30$) and overall survival (0.93, 0.81–1.08; $p=0.37$), and distant recurrences (0.93, 0.81–1.07; $p=0.29$) were much the same in both groups. Members noted a pre-specified analysis indicated that zoledronic acid improved IDFS in patients who were over 5 years since menopause at trial entry ($n=1041$; HR 0.77, 95% CI 0.63–0.96) but not in all other (premenopause, perimenopause, and unknown status) menopausal groups ($n=2318$; HR 1.03, 95% CI 0.89–1.20) but there was no statistically significant difference in overall survival for either the postmenopausal group or the other groups. Members also noted a cumulative incidence of osteonecrosis of the jaw of 1.7% in the patients treated with zoledronic acid.
- 5.10. The Committee considered that the contrasting results of ABCSG-12 and AZURE may be due to the differing populations and background treatments used in the two studies. Members noted a commentary piece published in 2012 that included authors of the two studies considered the possibility of the beneficial effect of zoledronic acid on survival being limited to a 'low estrogen environment'.
- 5.11. The Committee noted evidence from an abstract of an unpublished meta-analysis of 41 randomised trials comparing bisphosphonates to no bisphosphonates (placebo or open control) on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) presented by Coleman et al at the San Antonio Breast Cancer Symposium (SABCS) in December 2013. Members noted that results indicated that breast cancer recurrence was decreased by 1.7% at 10 years for on those on bisphosphonates, and distant recurrences were reduced by 1.3%. Members noted that in the postmenopausal subset use of bisphosphonates reduced the risk of bone metastases recurrence at 10 years by 2.9% and risk of breast cancer death by 3.1%. However, members considered that the abstract lacked sufficient detail to draw definitive conclusions, in particular members noted that the 'post-menopausal' group was undefined and there was limited detail on the type, and dosing schedules of bisphosphonates used. Members noted that the analysis was planned to be published which would provide more clarity on these issues in due course.
- 5.12. The Committee considered that overall there was insufficient evidence to support the funding of zoledronic acid at this time as questions remained regarding optimal dosing and populations to be treated. Members considered that there would likely be a class

effect for bisphosphonates in this setting in which case it may be appropriate to use cheaper and more convenient currently funded oral bisphosphonates, such as risedronate, rather than I.V. zoledronic acid. Members noted osteoporosis was a known risk factor for postmenopausal women receiving aromatase inhibitors, and as such these women have their bone health closely monitored. Members noted that a proportion of these patients would already be eligible to receive funded treatment with a bisphosphonate, including zoledronic acid inj 0.05mg per ml, 100 ml (Aclasta) for osteoporosis. Members noted that this proposal was for prophylactic zoledronic acid treatment to improve survival in patients with breast cancer and considered that the data for this indication was unclear at this time.

- 5.13. Members considered that whilst in the studies zoledronic acid associated osteonecrosis of the jaw was relatively infrequent (up to 2%), it was a serious side effect and may be a particular issue for Māori and Pacifica women who not only have a higher prevalence of breast cancer compared with NZ Europeans but may also have poorer dental health and lower access to dental services. The Committee considered that the application should be reviewed by CaTSOP for advice on these issues and the benefits of zoledronic acid or alternative bisphosphonates in this setting, including the meta-analysis if it has been published.

6. Nab-Paclitaxel for first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine

Application

- 6.1. The Committee reviewed an application from Specialised Therapeutics Limited requesting funding of nanoparticle albumin-bound (nab) paclitaxel (Abraxane) in combination with gemcitabine for first-line treatment of metastatic adenocarcinoma of the pancreas.

Recommendation

- 6.2. The Committee **recommended** that the application for funding of nab-paclitaxel (Abraxane) in combination with gemcitabine for first-line treatment of metastatic adenocarcinoma of the pancreas be declined.
- 6.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 6.4. The Committee noted that pancreatic cancer was the fifth most common cause of cancer death, accounting for approximately 5% of all deaths from cancer and that Māori generally show higher registration and mortality rates than non-Māori. Members noted that the majority of patients present with advanced disease at diagnosis, consequently, survival is generally poor with estimates of 5-year survival being less than 5% and median survival around 6 months without treatment.
- 6.5. The Committee considered that current standard treatment for advanced pancreatic cancer in New Zealand included single agent gemcitabine or combination chemotherapy with irinotecan, oxaliplatin and infusional 5-fluorouracil (FOLFIRINOX) or cisplatin, epirubicin, capecitabine/5-fluorouracil and gemcitabine (PEX/FG).

- 6.6. The Committee noted evidence for nab-paclitaxel comprised one randomised, open label, phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in 861 patients with metastatic adenocarcinoma of the pancreas (MPACT) (Von Hoff et al N Engl J Med 2013 369 (18):1691-703). Members noted that patients were randomised 1:1 to receive nab-paclitaxel at a dose of 125 mg/m², followed by gemcitabine at a dose of 1000 mg/m² on days 1, 8, 15, 29, 36, and 43, or to receive gemcitabine alone at a dose of 1000 mg/m² weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, all patients were administered treatment on days 1, 8, and 15 every 4 weeks. Members noted that 431 patients were assigned to nab-paclitaxel plus gemcitabine, and 430 to gemcitabine alone and treatment was continued until the patient experienced progressive disease (based on the investigator's assessment) or unacceptable toxicity.
- 6.7. The Committee noted that the primary endpoint, overall survival, was improved by 1.8 months by the addition of nab-paclitaxel with median overall survival of 8.5 months (95% confidence interval [CI] 7.89 to 9.53) in the nab-paclitaxel plus gemcitabine arm compared with 6.7 months (95% CI 6.01 to 7.23) with gemcitabine alone (hazard ratio (HR) for death 0.72, 95% CI 0.62 to 0.83; P<0.001). Members also noted 1.8 months longer progression free survival in the nab-paclitaxel–gemcitabine group than in the gemcitabine group, with a median of 5.5 months (95% C, 4.5 to 5.9) versus 3.7 months (95% CI 3.6 to 4.0) (HR for disease progression or death 0.69, 95% CI 0.58 to 0.82, P<0.001).
- 6.8. The Committee noted that nab-paclitaxel was associated with higher rates of grade 3 or higher neutropenia (38% in the nab-paclitaxel–gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%).
- 6.9. The Committee considered that overall there was moderate strength and good quality evidence demonstrating that nab-paclitaxel in combination with gemcitabine provided a small, 1.8 month, increase in overall survival and progression free survival compared with gemcitabine alone, however, members were concerned at the high rates of toxicity observed with nab-paclitaxel, in particular fatigue and neutropenia, noting that this patient population was often very sick.
- 6.10. The Committee considered that benefits and risks of nab-paclitaxel in combination with gemcitabine compared with other currently funded treatment options, FOLFIRINOX or PEX/FG, was not clear.
- 6.11. The Committee noted results from a randomised phase III study (Reni et al 2005 Lancet Oncol 6: 369-376) which compared PEFG with gemcitabine alone. Members noted that PEFG improved progression free survival by 1.9 months compared with gemcitabine but that PEFG was associated with increased rates of neutropenia and thrombocytopenia (43% vs 14%).
- 6.12. The Committee noted evidence from a randomised trial that evaluated the efficacy of FOLFIRINOX compared with gemcitabine in 342 patients with metastatic pancreatic cancer who had not previously been treated with chemotherapy. Members noted that FOLFIRINOX nearly doubled median overall survival (OS) compared with gemcitabine (11.1 months vs. 6.8 months, hazard ratio (HR) for death, 0.57; 95% confidence interval [CI] 0.45 to 0.73; P<0.001) (Conroy et al 2011 N Engl J Med;364:1817-25.).
- 6.13. The Committee considered that the 4.3 month OS improvement for currently funded FOLFIRINOX was more impressive than the 1.8 month improvement in OS for nab-paclitaxel. Members noted that FOLFIRINOX was associated with significant toxicities, including neutropenia, thrombocytopenia, diarrhoea, and sensory neuropathy and therefore its use was generally reserved for younger fitter patients, however, members considered that nab-paclitaxel also had significant toxicity issues which would mean it was not suitable for all patients.

- 6.14. The Committee considered that whilst there was evidence for a small benefit of nab-paclitaxel over gemcitabine alone members questioned if this benefit was clinically meaningful when considering the quality of life impacts of the side effects for treatment. Members also noted that nab-paclitaxel was more expensive than FOLFORINOX treatment that appeared to have better efficacy, albeit with its own toxicity issues.

7. Sunitinib for pancreatic neuroendocrine tumours (pancreatic NETS)

Application

- 7.1. The Committee reviewed an application from Pfizer for the funding of sunitinib (Sutent) for the treatment of well differentiated, unresectable pancreatic neuroendocrine tumour (pancreatic NET) in patients who are symptomatic (despite somatostatin analogues) or have documented disease progression.

Recommendation

- 7.2. The Committee **recommended** that the application for funding of sunitinib for the treatment of patients with well differentiated, unresectable pancreatic NET be deferred pending further advice from the Cancer Subcommittee of PTAC (CaTSoP). The Committee recommended that CaTSoP review the funding of both sunitinib and temozolomide for pancreatic NET.
- 7.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 7.4. The Committee noted that pancreatic neuroendocrine tumours (pancreatic NETs) are uncommon tumours arising in the endocrine cells of the pancreas, and that most cases are sporadic and non-functioning (not associated with a hormonal syndrome). Members noted that functioning NETs are characterised by the type of hormone secreted e.g. insulinoma, gastrinoma, glucagonoma or vasoactive intestinal peptidoma (VIPoma), which cause a variety of clinical syndromes.
- 7.5. The Committee noted that key evidence for sunitinib comprised a Phase III, multinational, randomised, double-blind, placebo-controlled study comparing the efficacy and safety of sunitinib administered daily at a dose of 37.5 mg (n=86) versus placebo (n=85) in patients with histologically or cytologically proven diagnosis of well-differentiated local, locally advanced or metastatic progressive pancreatic islet cell tumour (pancreatic NET) (study A6181111, Raymond E et al. N Engl J Med. 2011;364(6):501-513). Members noted that 69% of the patients enrolled had received prior systemic therapy including chemotherapy. Members noted that treatment was continued until disease progression, unacceptable toxicity or death and that at the time of disease progression, patients were un-blinded and if randomised to placebo were offered open-label sunitinib in one of two separate extension studies (A6181078 or A6181114).
- 7.6. The Committee noted that the study was designed to have a single interim analysis following 130 events with the option of stopping the study for efficacy based on the primary endpoint Progression Free Survival (PFS). However, members noted that the study was stopped early by the Data and Safety Monitoring Committee (DSMC) after 73 PFS events had been observed because of more serious adverse events and deaths in the placebo group as well as a difference in PFS favoring sunitinib. Median PFS was 11.4 months in the sunitinib group compared with 5.5 months in the placebo group

(hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; $P < 0.001$). Members noted that the HR for death was also statistically significant with 9 deaths in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (HR for death, 0.41; 95% CI, 0.19 to 0.89; $P = 0.02$). However, there was no overall difference in quality of life and more diarrhoea in sunitinib treated patients (59% vs. 39%). Members noted that objective response rates for sunitinib were 9.3%, with 2 complete responses and 6 partial responses compared with 0 for the placebo group. Members considered that the OR for sunitinib was very low compared with OR's of approximately 40% seen with sunitinib in renal cell cancer. Members noted that updated overall survival (OS) analyses were provided by the supplier in the form of CSR and unpublished presentations however members considered all are confounded by cross over.

- 7.7. The Committee considered that overall the strength and quality of the evidence provided for sunitinib was moderate, noting that the study was stopped early and confounded by cross over.
- 7.8. The Committee noted that PHARMAC had received a number of NPPA applications for the funding of alternative treatments for patients with NETs (including pancreatic NET). Members noted that the majority of NPPA applications were for streptozocin and more recently temozolomide.
- 7.9. The Committee considered that these NPPA applications suggested that in New Zealand the current standard of care for patients with pancreatic NET was likely capecitabine in combination with temozolomide (CAPTEM) funded via NPPA. Members noted that PHARMAC had requested a Pharmaceutical Schedule funding application for temozolomide from NPPA applicants but had yet to receive one. Members noted evidence for temozolomide provided by PHARMAC staff, and considered it was supportive of temozolomide use in this setting. The Committee requested further advice on temozolomide, and its likely place in therapy compared with sunitinib from the Cancer Treatments Subcommittee.

8. Obinutuzumab for first line treatment of Chronic Lymphocytic Leukaemia

Application

- 8.1. The Committee reviewed a funding application from Roche for obinutuzumab (Gazyva) as first-line treatment in patients with chronic lymphocytic leukaemia (CLL) who have comorbidities preventing treatment with fludarabine, cyclophosphamide and rituximab (FCR).

Recommendation

- 8.2. The Committee **recommended** that obinutuzumab is funded with medium priority for patients with chronic lymphocytic leukaemia who have comorbidities preventing treatment with fludarabine, cyclophosphamide and rituximab. The Committee also **recommended** that this funding application is provided to the Cancer Subcommittee of PTAC (CaTSoP) for review including for advice on: (i) what proportion of patients are currently receiving chlorambucil monotherapy, (ii) how the overall CLL treatment paradigm would be affected by the funding of obinutuzumab, and (iii) appropriate Special Authority funding restriction criteria for obinutuzumab.
- 8.3. The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iii) *The clinical benefits and risks of pharmaceuticals and* (iv) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 8.4. The Committee noted that the main evidence supplied was a SIGN 1+ open-label randomised controlled trial (RCT), sponsored by Roche (Goede V et al. *N Engl J Med* 2014; 370: 1101-10). The Committee noted that in the study, there was probably masked assessment of some outcomes but not for the primary outcome. The Committee noted that all participants of the study had previously untreated CLL who had comorbidities and estimated Glomerular Filtration Rates (eGFR) between 20 and 69 ml/min. The median age of participants was 74 years with about 25% of patients aged <65 years and 60% of participants were male. The Committee noted that the median ECOG (Eastern Cooperative Oncology Group) was 1. The Committee also noted that the main patient comorbidities were cardiovascular conditions including heart and vascular disease as well as hypertension.
- 8.5. The Committee noted that for the primary outcome, median progression free survival (PFS) in the obinutuzumab plus chlorambucil arm (OBZ-CHL) was 27 months compared to 15 months in the rituximab plus chlorambucil arm (RTX-CHL) arm and 11 months in the chlorambucil arm (CHL). These results were statistically significant with the following hazard ratios (HR):
- OBZ-CHL versus CHL HR 0.18, 95% CI 0.13 to 0.24, $P < 0.001$;
 - RTX-CHL versus CHL HR 0.44; 95% CI, 0.34 to 0.57, $P < 0.001$; and
 - OBZ-CHL versus RTX-CHL HR 0.39; 95% CI, 0.31 to 0.49, $P < 0.001$.
- 8.6. The Committee considered that for the primary outcome, the median length of follow-up was unclear but based on the survival plots, it appears that it was 18 months for both the OBZ-CHL and RTX-CHL arms and 21 months for the CHL arm. The Committee noted that the death rates in the larger full group of patients in the OBZ-CHL and RTX-CHL arms were 8% and 12% respectively. In the groups followed up for a shorter period, death rates in the OBZ-CHL, RTX-CHL and CHL groups were 9%, 15% and 20% respectively with HRs of 0.41 (95% CI 0.23-0.74) when OBZ-CHL was compared to CHL and 0.66 (95% CI 0.41 to 1.06) when OBZ-CHL was compared to RTX-CHL.
- 8.7. The Committee noted that the Goede V et al study states without quantitative summaries that quality of life (QOL) was the same in all groups although it was only measured up until disease progression. The Committee considered that the most prominent adverse reactions were infusion reactions and neutropenia which were common in the OBZ-CHL arm at about 20% and 35% respectively.
- 8.8. The Committee considered that currently in New Zealand, first-line treatments in CLL included FCR in fitter adults without significant comorbidities whilst CHL monotherapy was given to older, less fit adults. Haematopoietic stem cell transplantation is also considered in some high risk genetic situations. The Committee considered that if OBZ was funded, it would be used in combination with CHL. The Committee noted that although there was no direct evidence comparing RTX and OBZ based regimes in patients otherwise eligible for FCR, it is likely that some patients currently eligible for FCR would be treated with OBZ-based regimes instead based on the indirect evidence available to date.
- 8.9. The Committee considered that the patients most likely to benefit from treatment with OBZ were adults currently unsuitable for FCR with moderate comorbidity with eGFR between 30 and 69 ml/min. The Committee also considered that the supplier's assumption that 30% of 'watch and wait' CLL patients would die of other causes before treatment was quite high. The Committee considered that it would be more appropriate to assume that 4% of 'watch and wait' CLL patients would die of other causes per year based on the 18% death rate over a 5.7 year follow-up period in the Gentile M et al study (*Br J Haematology* 2014; 167: 224-32). The Committee noted that in their budget impact estimates, the supplier had failed to take account of 'watch and wait' patients from prior years, not just watch and wait patients who were newly diagnosed each year.

The Committee considered that it would be reasonable to assume that between 7 to 9% of 'watch and wait' patients (including those from previous years) would require treatment per year (Molica S et al. Cancer 2013; 119: 1177-85 and Gentile M et al. American Journal of Hematology 2014; 89: 743-50).

- 8.10. The Committee considered that the budget impact analysis completed by the supplier was likely an underestimate and noted that the estimate completed by PHARMAC staff was more realistic. The Committee also noted that there is a fiscal risk associated with the funding of this product as it would potentially be preferred over rituximab for CLL patients who are not contraindicated to FCR and for other indications rituximab is currently funded for.
- 8.11. The Committee considered that if funded, OBZ should be restricted by criteria similar to that for rituximab currently but for patients who have contraindications to FCR. The Committee noted that contraindications to FCR are difficult to define but could be based on the Goede et al 2014 study criteria with specific important comorbidities a requirement for eGFR to be between 30 and 69 ml/min.

9. Amifostine for the prevention of cisplatin related ototoxicity in low and intermediate risk medulloblastoma patients

Application

- 9.1. The Committee reviewed an application from a clinician for the funding of amifostine for the prevention of cisplatin related ototoxicity in low and intermediate risk medulloblastoma patients.

Recommendation

- 9.2. The Committee **recommended** that the application for the funding of amifostine on the Pharmaceutical Schedule for the prevention of cisplatin related ototoxicity be declined.
- 9.3. The Committee **recommended** that amifostine should be funded for the prevention of cisplatin related ototoxicity for paediatric low and intermediate risk medulloblastoma patients participating in a randomised clinical trial sponsored by St Jude's Children's Research Hospital.
- 9.4. The Committee **recommended** that PHARMAC review the mechanisms through which unfunded clinical trial treatments and paediatric oncology treatments are reviewed and funded.
- 9.5. 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.*

Discussion

- 9.6. The Committee noted medulloblastoma is the most common malignant brain tumour of childhood. The Committee further noted that the addition of platinum-based chemotherapy to postoperative craniospinal irradiation has increased cure rates for patients with localised, resected medulloblastomas to more than 80% and permitted reduction in the dose of craniospinal irradiation. However, members noted that cisplatin is a potent ototoxin that causes cochlear hair cell destruction and that a high proportion of patients given cisplatin develop permanent bilateral sensorineural hearing loss, with young children being most susceptible. Members further noted that amifostine was a prodrug which is metabolised in humans to WR-1065, a thiol-reducing agent and potent free-radical scavenger which had demonstrated otoprotective properties against cisplatin in experiments using hamsters and guinea pigs.

- 9.7. The Committee noted that a St Jude's medulloblastoma study, SJMB12, has been recruiting since June 2013 and includes New Zealand sites. Members noted that the study protocol requires use of amifostine for average risk patients but not high risk and noted that the clinician applicant wished to enrol patients in this study and that that was the primary reason for the application.
- 9.8. The Committee noted evidence supplied by the applicant in support of the application comprised a paper by Gurney et al; *Neuro-Oncology* 2014;0:1-8 from St Jude's Children's research hospital describing observational data from 379 medulloblastoma patients enrolled in two sequential studies SJMB96 (which enrolled from 1996 to 2003) and SJMB03 (which started enrolment in 2003). Members noted that all patients in SJMB03 received amifostine but that SJMB96 protocol was amended towards the end of the recruitment period (in 1999) to include amifostine administration although no randomisation was undertaken. Members noted the studies enrolled 263 patients with average-risk medulloblastoma and 116 patients with high-risk medulloblastoma, and the analysis compared hearing loss in 328 patients who received amifostine with 51 patients enrolled in the early part of SJMB03 who did not.
- 9.9. The Committee noted that the authors reported that among the average-risk medulloblastoma patients amifostine was associated with protection from serious hearing loss (adjusted odd ratio (OR), 0.30; 95% CI, 0.14–0.64) but not in high-risk medulloblastoma patients (OR, 0.89; 95% CI, 0.31–2.54).
- 9.10. The Committee also noted a publication of an analysis of the average-risk patients enrolled in the SJMB96 study (n=87) (Fouladi et al; *J Clin Onc* 2008;26:3749-3755). Members noted that of the 75 patients that had audiology exam at year one 13/35 (37%) of the patients who didn't receive amifostine and 9/40 (22%) with amifostine had at least grade 3 or 4 ototoxicity (P=0.005).
- 9.11. The Committee considered that the strength and quality of the evidence was weak noting that the relevance of combining data from the two trials was uncertain as they were unrandomised and undertaken over different time periods. The Committee further noted the unexplained difference reported between the average risk and high risk patients, with no protective effect on hearing loss in the high risk group. The Committee noted the authors considered the results for the high risk group may be falsely negative due to sparse data.
- 9.12. The Committee noted that the positive findings from the observational studies SJMB96 and SJMB03 were at odds with the findings in two randomised controlled trials of amifostine in patients receiving platinum chemotherapy with hepatoblastoma (Katzenstein et al; *Cancer* 2009; 115:5828-35) and osteosarcoma (Gallegos-Castorena receiving Paed Haem and Onc 2007; 24:403-408) and Osteosarcoma. Members noted that in these two randomised studies amifostine had no protective effect on audiological toxicity.
- 9.13. The Committee noted Cochrane review (Van AS et al 2014) which concluded that at this time, there is insufficient evidence to support the use of amifostine as an otoprotective intervention. The Committee also noted guidelines published by the American Society of Clinical Oncology (Hensley et al 2008 *J Clin Oncol* 27:127-145) that state that amifostine is not recommended for prevention of platinum-associated ototoxicity.
- 9.14. The Committee concluded that overall there was insufficient evidence to support the routine use of amifostine for prevention of ototoxicity in patients receiving platinum chemotherapy. The Committee considered its routine use in St Jude's clinical trials appeared inconsistent with other clinical trials and other centres internationally. The Committee did not support the funding of amifostine on the Pharmaceutical Schedule for the prevention of ototoxicity. However, members were supportive of patients, children in particular, being enrolled in clinical trials and noted the difficult situation faced by the applicant who wished to participate in the St Jude's SJMB12 clinical trial that required

amifostine administration. Noting the low overall cost of amifostine treatment in this limited situation of participation in a clinical trial the Committee was supportive of amifostine being funded for patients enrolled in the SJMB12 clinical trial.

10. Aflibercept for neovascular (wet) age-related macular degeneration

Application

- 10.1. The Committee reviewed an application from Bayer NZ Ltd and a clinician for the listing of aflibercept on the Hospital Medicines List (HML) for the treatment of neovascular (wet) age-related macular degeneration (wAMD).

Recommendation

- 10.2. The Committee **recommended** that PHARMAC run a Request for Proposals for second line anti-vascular endothelial growth factor (anti-VEGF) treatment of wAMD following bevacizumab treatment.
- 10.3. The Committee **recommended** that depending on the outcome of a competitive process, aflibercept or ranibizumab be listed on the HML subject to the following restriction criteria:

Initiation

Re-assessment required after 3 doses

Both:

1. Either
 - 1.1 Wet age-related macular degeneration (AMD); or
 - 1.2 Polypoidal choroidal vasculopathy; or
 - 1.3 Choroidal neovascular membrane from causes other than wet AMD; and
2. Either:
 - 2.1 The patient has had a severe ophthalmic inflammatory response following bevacizumab; or
 - 2.2 Treatment with bevacizumab has proven ineffective following at least three intraocular injections.

Continuation

Re-assessment required at 6 months, 12 months and 24 months from initiation of treatment, then 2 yearly thereafter.

Both:

1. Documented benefit must be demonstrated to continue; and
 2. In the case of previous non-response to bevacizumab, a re-trial of at least one dose of bevacizumab is required at 6 months, 12 months and 24 months to confirm non-response before continuing with aflibercept.
- 10.4. The Committee deferred making a recommendation regarding the funding of a third line anti-VEGF agent for wAMD at this time, pending the outcome of a competitive process for second and third line treatment for wAMD. The Committee will reconsider its view on the funding of a third line anti-VEGF agent for wAMD after the competitive process has been run and it is known which agent would potentially be funded as the second line treatment option and the cost-utility analysis of funding the alternative agent in the third line setting has been updated.
- 10.5. 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; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 10.6. The Committee noted wAMD is the commonest cause of blindness and it affects 1 in 7 people over the age of 50. Members noted the incidence of AMD increases with age; it is estimated by the age of 80, one in four New Zealanders have vision loss from AMD. The Committee noted risk factors include smoking, alcohol consumption and obesity. Members noted rates of vision loss from wAMD are reported to be higher in Māori.
- 10.7. The Committee noted the currently funded treatments listed on the HML for wAMD are intravitreal bevacizumab and intravitreal ranibizumab. Members noted these anti-vascular endothelial growth factor (VEGF) treatments require administration in the hospital setting. Members noted aflibercept is another anti-VEGF agent with a different molecular structure to ranibizumab.
- 10.8. The Committee noted the minutes and recommendation of the Ophthalmology Subcommittee of PTAC meeting in October 2014. Members noted that in New Zealand, patients were often treated for wAMD with either intravitreal bevacizumab or ranibizumab using a 'treat and extend' protocol where treatment intervals were extended out as long as possible while at the same time ensuring that the disease remained controlled. Members considered this typically meant that patients received on average 6 to 8 doses per year.
- 10.9. The Committee noted the funding application for aflibercept was for second line treatment as an alternative to ranibizumab. However, members also noted PHARMAC had received several Named Patient Pharmaceutical Assessment applications for individual patients requesting aflibercept as a third line agent, following previous treatment with bevacizumab and ranibizumab. Members noted PHARMAC has declined NPPA applications for third line treatment due to significant budget impact and because it was considered more appropriate to consider this large group under the usual Schedule listing process.
- 10.10. The Committee noted the results from two Phase III head-to-head multicentre randomised controlled trials of aflibercept and ranibizumab, VIEW 1 and VIEW 2 (Schmidt-Erfurth et al. *Ophthalmology* 2014;121:193-201; Heier et al. *Ophthalmology* 2012;119:2537-48). Members noted 2400 patients were randomized to intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, 2 mg every 2-months after 3 initial monthly doses, or ranibizumab 0.5 mg monthly for 52 weeks. Members noted that after the 52-week primary end point, a follow-up phase up to 96 weeks was based on switching the aflibercept dosing regimen to a 'treat and extend' protocol, however for ranibizumab a 4-weekly dosing regimen was continued. Members noted this does not reflect clinical practice in New Zealand for ranibizumab. Members considered the study populations were different to the New Zealand population as they were treatment naïve. The Committee noted that these studies indicated that aflibercept given every 8 weeks was as effective as ranibizumab given 4-weekly in improving visual acuity outcomes, but with an average of 5.3 fewer injections after 96 weeks. The proportion of subjects with maintained vision at week 52 was >94% in all four treatment groups; largely similar proportions of patients (91.5% to 92.4%) maintained visual acuity across all treatment groups at week 96. All aflibercept treatment groups were numerically similar, and proven to be non-inferior to ranibizumab every 4-weeks, in the proportion of subjects maintaining vision. The Committee noted adverse effects profiles were similar between the two agents.
- 10.11. Members noted the 2013 NICE aflibercept report (NICE technology appraisal 294, July 2013, www.nice.org.uk) that included a network meta-analysis comparing aflibercept with ranibizumab in a "treat and extend" regimen. Members noted this analysis demonstrated no statistically significant differences between aflibercept fixed dose 2mg every 8 weeks/treat as needed and ranibizumab 0.5mg treat as needed regimens.

- 10.12. The Committee also noted additional evidence supplied by the clinician: Patel et al (Eye 2013;27:663-8) a case-series of three patients describing the efficacy of aflibercept in patients with wAMD refractory or with tachyphylaxis to bevacizumab and ranibizumab treatments; and Kumar et al (Retina 2013; 33:1605-12), a retrospective study of 33 patients assessing the efficacy of intravitreal aflibercept in patients with neovascular age-related macular degeneration resistant to ranibizumab.
- 10.13. The Committee noted the Ophthalmology Subcommittee was supportive of aflibercept and this was in part based on clinical opinion that aflibercept may be superior to ranibizumab. The Committee noted there is no evidence currently available of superiority of aflibercept over ranibizumab for wAMD. The Committee noted patients may require less visits to hospital for treatment with aflibercept treatment and this could be advantageous. Members noted aflibercept is more like bevacizumab than ranibizumab in terms of systemic exposure and this may be relevant in terms of clinical risk for some patients (e.g. pregnancy, stroke).
- 10.14.  The Committee also noted ranibizumab is not currently under contract with PHARMAC and the price is anticipated to decrease in the future, particularly when ranibizumab biosimilars are expected to enter the market. The Committee considered that bevacizumab should remain the first-line treatment option given its good cost-effectiveness relative to aflibercept and ranibizumab. The Committee considered there is no clinical reason not to run a competitive process between aflibercept and ranibizumab for second line treatment of wAMD.
- 10.15. Members also noted access to anti-VEGF treatment is limited for some patients due to location, access to specialists or ability to attend hospital clinics. The Committee noted there is uncertainty with a definition of non-response to treatment and some patients continue to receive treatment despite minimal benefit. This makes it difficult to determine how many patients would require second and third line treatment. The Committee considered 8-10 % of the patients treated with bevacizumab for wAMD would require a second line treatment.
- 10.16. The Committee noted the result of the Cost Utility Analysis for third line treatment of wAMD. The Committee considered third line treatment may be necessary for a small group of patients, however this would be dependent on which agent was used second line and the cost of treatment. The Committee noted funding a third line agent for all patients would have significant budget impact and deferred making a recommendation regarding the funding of a third line anti-VEGF agent for wAMD at this time pending the outcome of a potential competitive process in this market.
- 10.17. Members noted VEGF agents can also be used for the treatment of diabetic macular oedema and this is another large patient group that requires assessment. The Committee noted diabetic macular oedema is a Medsafe approved indication for aflibercept and ranibizumab and PHARMAC are expecting funding applications for this indication.

11. Cinacalcet for hyperparathyroidism

Application

- 11.1. The Committee noted a memorandum from PHARMAC staff regarding cinacalcet for the treatment of hyperparathyroidism. The Committee noted that this paper originated from a 2008 PHARMAC paper generated in light of a number of Exceptional Circumstances (EC) applications for this pharmaceutical and that this situation persists today, with 45 applications for cinacalcet since 2012 when the EC scheme was replaced by Named Patient Pharmaceutical Assessment (NPPA).

Recommendation

- 11.2. The Committee **recommended** to decline listing cinacalcet in Section B or Part II Section H of the Pharmaceutical Schedule but that it should remain available to be funded through the NPPA scheme and that applications for cinacalcet are reviewed by panel members for approval.
- 11.3. The Decision Criteria particularly relevant to this recommendation are: *i.) The health needs of all eligible people within New Zealand; ii.) The particular health needs of Maori and Pacific peoples; iv.) The clinical benefits and risks of pharmaceuticals; v) The budgetary impact (in terms of the pharmaceutical budget and the Governments overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 11.4. The Committee noted that this paper was being discussed due to the number of NPPA applications that continue to be generated for cinacalcet as opposed to this paper being generated by the supplier. Members noted that since 2012 when the NPPA process had replaced the EC scheme there had been there had been 45 applications for cinacalcet, and 41 of these had been approved under the Urgent Assessment pathway. Members noted that applicant requests for access to cinacalcet were unevenly distributed throughout the country and the indications varied from primary to secondary and tertiary hyperparathyroidism.
- 11.5. The Committee noted that PHARMAC staff had developed a set of criteria, approved by the decision maker to guide assessment of cinacalcet NPPA applications and that currently applications were assessed using the criteria and individual applications were no longer routinely presented to NPPA panel members for their review.
- 11.6. The Committee noted the recommendations of the Endocrinology and Nephrology Subcommittees of PTAC from their 2014 meetings. The Committee noted the recommendation by the Endocrinology Subcommittee 'that cinacalcet be available for patients with PHPT who have significant/symptomatic hypercalcaemia (>3mmol/L) and can't be treated surgically (after consultation at a centre of excellence in head and neck surgery)' and considered that the contraindication for surgical treatment for patients with primary hyperparathyroidism would be very rare. The Committee considered the Special Authority criteria the Nephrology Subcommittee had drafted at their recent meeting and agreed with the criteria 'that cinacalcet be prescribed for the indication of calciphylaxis'. The Committee further considered that the criterion 'that patients with severe unremitting secondary hyperparathyroidism not successfully treated surgically could be prescribed cinacalcet only if symptomatic' required further development.
- 11.7. The Committee considered that the new clinical evidence was not supportive of listing cinacalcet for hyperparathyroidism. Members noted that the two pivotal studies for cinacalcet were the Evolve Trial (NEJM 2012, DOI: 10.1056/NEJMoa1205624) and the ADVANCE study (Raggi et al. Nephrol Dial Transplant 2011;26(4):1327-39).
- 11.8. The Committee noted the Evolve Randomized Control Trial (RCT) compared the effects of cinacalcet versus placebo in addition to traditional therapy (such as phosphate binders and vitamin D sterols) to treat moderate to severe secondary hyperparathyroidism in patients on haemodialysis. Members considered that the primary composite outcome was mortality and major cardiovascular events and that among patients in the cinacalcet group, there was a non-significant reduction in the primary composite endpoint of 7% (OR 0.93, 95% CI 0.85-1.02, p = 0.11) in the Intention to Treat analysis and no clinical benefit was shown. Members noted the only significant outcome measure was reduced rate of parathyroidectomy; however the benefit of this is not clear as surgical technologies are rapidly evolving. Members considered that despite the lack of benefit shown this was a good study design.

- 11.9. The Committee noted that the 2012 NEJM Evolve editorial reported that “the non-significant relative reduction in the primary outcome of 7% (odds ratio 0.93; 95% confidence interval, 0.85 – 1.02) was disappointing, particularly given the huge effort involved in conducting the study.”
- 11.10. The Committee noted the Advance RCT 2011 comparing the progression of vascular and cardiac valve calcification in 360 patients with secondary hyperparathyroidism treated with cinacalcet plus low-dose vitamin D sterols or flexible doses of vitamin D sterols alone. Members considered the primary endpoint was percentage change in Agatston coronary artery calcification from baseline to week 52. Members noted Median Agatston CAC scores increased 24% in the cinacalcet group and 31% in the flexible vitamin D group (P= 0.073). Corresponding changes in volume CAC scores were 22 and 30% (p = 0.009). Members noted the clinical relevance of this outcome was unknown.
- 11.11. The Committee noted that the Australian Pharmaceutical Benefits Advisory Committee (PBAC) at its November 2014 meeting considered that cinacalcet would not be cost-effective at \$45,000 - \$75,000 cost per QALY gained. Members noted that at the 2014 meeting PBAC suggested delisting cinacalcet from the Pharmaceutical Benefits Scheme (PBS).
- 11.12. The Committee noted, as demonstrated by quality RCT evidence, that overall there is no cardiovascular benefit or improved management of severe bone pain for patients receiving cinacalcet. Members considered that compared with placebo, cinacalcet may reduce the need for parathyroidectomy.
- 11.13. The Committee considered that the additional health benefit may extend to those with secondary hyperparathyroidism waiting for surgery. Members noted that since 2012 four NPPA applications had also been approved for calciphylaxis and considered this was an appropriate indication.
- 11.14. The Committee considered that at their next meeting the Endocrinology Subcommittee of PTAC should develop clear criteria for funding cinacalcet for the subset of patients with primary and secondary hyperparathyroidism with severe symptoms due to hypocalcaemia who are unable to tolerate surgery as determined by a specialist head and neck surgeon and calciphylaxis.

12. Buprenorphine sublingual tablets (Subutex) in pregnancy and breastfeeding

Application

- 12.1. The Committee considered submissions from clinicians in support of the funding of buprenorphine sublingual tablets (Subutex) in women receiving buprenorphine with naloxone sublingual tablets (Suboxone) for opioid addiction who subsequently become pregnant.

Recommendation

- 12.2. The Committee **recommended** that the application to fund buprenorphine sublingual tablets (Subutex) in women receiving buprenorphine with naloxone sublingual tablets (Suboxone) for opioid addiction who subsequently become pregnant be declined. The Committee also **recommended** that Subutex should not be funded for use in breastfeeding women.
- 12.3. The Decision Criteria particularly relevant to this recommendation are: *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

- 12.4. The Committee noted that buprenorphine sublingual tablets (hereafter referred to as Subutex) are not registered with Medsafe for use in New Zealand, whereas buprenorphine with naloxone sublingual tablets (hereafter referred to as Suboxone) is registered for the treatment of opiate dependence, within a framework of medical, social and psychological treatment. The Committee noted that the key difference between Subutex and Suboxone is that Suboxone contains naloxone, which is included for the sole purpose of deterring intravenous misuse of buprenorphine sublingual tablets.
- 12.5. The Committee noted that in July 2013 the Mental Health Subcommittee had considered the funding of Subutex in pregnant women receiving Suboxone for opioid addiction, in the following three groups of patients:
1. Women who are stabilised on funded Suboxone and become pregnant
 2. The same women as in 1, above, who then breastfeed
 3. Patients eligible for Suboxone funding who are allergic to naloxone
- 12.6. The Committee noted the Subcommittee's view that the evidence for using Subutex instead of Suboxone or methadone in pregnant or breastfeeding women is weak and does not outweigh the risk of abuse (relapse to intravenous opioid use), diversion and discontinuation from Subutex. Therefore, the Subcommittee recommended that the application to fund Subutex for women on Suboxone who become pregnant or are breastfeeding be declined. The Subcommittee also recommended that the funding of Subutex in patients who are allergic to naloxone be declined. The Committee noted it had previously reviewed the Subcommittee's minutes and accepted the recommendations made by the Subcommittee.
- 12.7. The Committee noted that PHARMAC has subsequently received submissions from a clinician and from the National Association of Opioid Treatment Providers (NAOTP) requesting reconsideration of funding of Subutex in women stabilised on Suboxone who become pregnant.
- 12.8. The Committee noted that the patient numbers would likely be low (in the region of 8-10 women per year) and considered that patients would likely be on treatment for approximately 6-12 months, assuming they switched back to Suboxone following the end of pregnancy. The Committee considered that the dosing regimen for Subutex would be the same as for Suboxone. The Committee considered that if Subutex was also available for women planning pregnancy, patient numbers would be higher with a longer duration of treatment.
- 12.9. The Committee noted the most frequently cited publication in support of the use of Subutex in pregnant opioid-dependent women, the MOTHER study (Jones et al. N Engl J Med 2010;363:2320-31), which had previously been reviewed by the Subcommittee. This was a double-blind, randomised, placebo controlled trial comparing the use of methadone and buprenorphine initiated in 175 opioid-dependent pregnant women who were being commenced on opioid maintenance treatment. For the patients who delivered during the study, there were no statistically significant differences in total neonatal abstinence syndrome (NAS) score, peak NAS score, the percentage of neonates requiring NAS treatment, or head circumference. There was a statistically significant difference in favour of buprenorphine for the amount of morphine required to manage NAS, duration of hospital stay and duration of NAS treatment. The Committee noted that the patient group in the study was different from the group being considered for PHARMAC funding, as the women in the study were initiated on treatment during pregnancy, rather than switching from Suboxone.
- 12.10. The Committee noted a review article by the same authors (Jones et al. Addiction 2012;(Suppl 1):5-27) that suggests that maternal treatment with buprenorphine has comparable efficacy to methadone, with some foetal outcomes possibly better with buprenorphine. However, in the largest study reviewed more patients dropped out of

buprenorphine treatment than methadone during pregnancy and it is unknown what the outcomes were for these women.

- 12.11. The Committee noted a Cochrane Review (Minozzi et al. Cochrane Database Syst Rev. 2008;16;CD006318) that did not find sufficient significant differences between methadone and buprenorphine to conclude that one treatment is not superior to another in pregnant women. The authors noted that while methadone seems superior in terms of retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndrome.
- 12.12. The Committee noted an Up to Date article (Berghells et al Up to Date October 2014), a review overlaid with clinical opinion, in which the authors state that Subutex remains the preferred formulation (versus Suboxone) for pregnant patient and that women on Suboxone should be switched to Subutex if possible. However, the authors note that available evidence with Suboxone in pregnancy is reassuring and that Suboxone should not be withheld from pregnant patients in areas without access to Subutex or methadone.
- 12.13. The Committee noted that the recommendation in the World Health Organization Guidelines for the identification and management of substance use and substance use disorders in pregnancy (2014) that “Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine” is accompanied by a Remark that “In opioid-dependent pregnant women, the buprenorphine mono formulation should be used in preference to the buprenorphine/naloxone formulation.” The Committee noted that no evidence was cited to support this remark and the Guideline document rated the quality of evidence for the recommendation as “very low.”
- 12.14. The Committee noted that regulatory pregnancy categories, contraindications, warnings and precautions were generally the same for buprenorphine as for buprenorphine with naloxone in New Zealand, Australia, the UK and the US, although there were some differences between countries.
- 12.15. The Committee noted that clinicians generally recommend against switching between buprenorphine (with or without naloxone) and methadone in pregnancy because of the risk of destabilising or causing withdrawal symptoms in the mother or foetus.
- 12.16. The Committee considered that the evidence for Subutex in pregnant opioid-dependent women was generally weak and of poor quality. The Committee considered that there was a lack of evidence comparing outcomes and safety between Suboxone and Subutex in pregnancy, and noted that no evidence had been provided supporting the benefits of switching from Suboxone to Subutex in pregnant women stabilised on Suboxone.
- 12.17. The Committee noted that naloxone is not contraindicated for use in pregnancy and breastfeeding in New Zealand, although pregnancy and lactation is noted under the warnings and precautions on the Medsafe datasheet. The Committee noted that only very low quantities of naloxone reach circulation in humans following sublingual administration, and these do not remain in the system for long. The Committee noted that the effect of this small amount of naloxone on the foetus is unknown; however, the Committee considered that this would likely be minimal compared with the potential significant deleterious effects of buprenorphine, alcohol or other (potentially illicit) drugs the foetus may be exposed to.
- 12.18. The Committee considered that Subutex is associated with an unacceptably high risk of abuse and diversion generally, which is of particular concern in the patient group under consideration given the high risk of abuse and diversion in this patient group. The Committee noted that in the MOTHER study, despite being paid to be abstinent, 33% of

the buprenorphine group and 23% of the methadone group tested positive for illicit opioids during the study (among completers).

- 12.19. Overall, the Committee considered that given Subutex's high abuse potential, its unregistered status (with associated pharmacy procurement costs that may be passed on to the patient) in addition to the possible increase in use of 'consume on premises' doses (and therefore increased dispensing costs) and lack of evidence that switching from Suboxone to Subutex would be likely to significantly positively affect outcomes for the mother and foetus, the application to fund Subutex should be declined.

13. Benzbromarone and febuxostat Special Authority criteria

Application

- 13.1. The Committee considered information from a supplier and the Rheumatology Subcommittee of PTAC in relation to the Special Authority criteria and Hospital Medicines List (HML) criteria for benzbromarone (Benzbromaron AL 100) and febuxostat (Adenuric).

Recommendation

- 13.2. The Committee **recommended** that the Special Authority criteria for febuxostat be amended as follows (additions in bold, deletions in strikethrough), and that the HML criteria be amended in the same way, with a high 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 up to 900 mg/day** and ~~appropriate doses of~~ **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 ~~appropriate doses of~~ **use of** probenecid **at doses of up to 2 g per day or maximum tolerated dose;** or
 - 2.3 ~~Both:~~
- 3.1 ~~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 Notes); ~~and~~
- 3.2 ~~The patient has a rate of creatinine clearance greater than or equal to 30 ml/min.~~

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

Notes: **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.

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

Special Authority for Subsidy

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

All of the following:

- 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 up to 900 mg/day** and ~~appropriate doses of~~ **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 ~~appropriate doses of~~ **use of** probenecid **at doses of up to 2 g per day or maximum tolerated dose**; or
 - 2.3 Both:
 - 2.3.1 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 Notes); and
 - 2.3.2 The patient has a rate of creatinine clearance greater than or equal to 20 ml/min.
 - 2.4 All of the following:
 - 2.4.1 The patient is taking azathioprine and requires urate-lowering therapy; and
 - 2.4.2 Allopurinol is contraindicated; and
 - 2.4.3 Appropriate doses of probenecid are ineffective or probenecid cannot be used due to reduced renal function; and
- 3 The patient is receiving monthly liver function tests.

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

Notes: Benzbromarone has been associated with potentially fatal hepatotoxicity.

In chronic renal insufficiency, particularly when the glomerular filtration rate is 30 ml/minute or less, probenecid may not be effective. 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.

The New Zealand Rheumatology Association has developed information for prescribers which can be accessed from its website at www.rheumatology.org.nz/downloads/Benzbromarone-prescriber-information-NZRA-V2.pdf

- 13.4. The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand*; (ii) *The particular health needs of Māori and Pacific peoples*; (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things*; (iv) *The clinical benefits and risks of pharmaceuticals*.

Discussion

- 13.5. The Committee noted that the Rheumatology Subcommittee of PTAC had recommended changes to the benzbromarone and febuxostat Special Authority criteria at its October 2014 meeting.
- 13.6. The Committee reviewed the information that had been reviewed by the Subcommittee, including submissions from TeArai BioFarma, the supplier of febuxostat.
- 13.7. The Committee considered that the changes to the Special Authority for febuxostat and benzbromarone recommended by the Subcommittee were appropriate, with some additional amendments as discussed below.
- 13.8. The Committee noted that in February 2014 PTAC had recommended that the criteria for febuxostat include a requirement that the patient has had three or more confirmed

episodes of symptomatic gout but this had not been included in the final Special Authority when febuxostat was funded in June 2014. The Committee considered that it was important to require a diagnosis of gout in both the febuxostat and benzbromarone restrictions, noting that the Committee had only ever reviewed the use of these agents for the treatment of gout.

- 13.9. The Committee noted reports of the use of febuxostat in patients with renal impairment (Sakai et al. *Ren Fail* 2014;36(2):225-231; Filiopoulos et al. Poster at 50th Congress of the European Renal Association and European Dialysis and Transplant Association 2013; Horikoshi et al. *Clin Exp Nephrol* 2013;17:149-50; Saag & Kenneth. Abstract at American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting 2013;Abstract 1178) provided by the supplier. The Committee noted that there are other reports of the use of febuxostat in patients with renal failure, mainly from Japan. The Committee considered that the value of febuxostat in preventing gout in this situation is not very clear as most patients appeared to be treated for hyperuricaemia rather than gout. However, the Committee considered that there was no compelling reason to retain the creatinine clearance criterion for febuxostat, provided that the information on febuxostat's Medsafe datasheet regarding the use of febuxostat in renal impairment is included as a note on the Special Authority form.
- 13.10. The Committee noted that allopurinol is used in patients with renal impairment including those on dialysis and that this use was supported by the Nephrology Subcommittee (December 2014).
- 13.11. The Committee noted that the Medsafe datasheet for probenecid only mentions ineffectiveness of probenecid at creatinine clearance less than 30 ml/min. The Committee considered that it would be useful for this information to be included in the note for both febuxostat and benzbromarone.
- 13.12. The Committee agreed with the Rheumatology Subcommittee that it was reasonable to retain the criterion defining creatinine clearance cut-off in the benzbromarone Special Authority given its mode of action and lack of evidence of benefit below creatinine clearance 20 ml/minute.
- 13.13. The Committee noted that the allopurinol datasheet and international guidance (e.g. Rider & Jordan, *Rheumatology* 2010;49:5-14) allow for the use of allopurinol up to 900 mg per day. The Committee considered that it would be useful to include this maximum in the Special Authority criteria for both febuxostat and benzbromarone.
- 13.14. The Committee considered that the proposed changes would be unlikely to alter the use of funded benzbromarone but removal of the creatinine clearance cut off from the febuxostat criteria potentially increase the number of funded febuxostat patients, although it was difficult to say by how much. The Committee considered that any increase may be limited by the other proposed changes to the febuxostat criteria.

14. Rituximab as a second-line biologic treatment for polyarticular juvenile idiopathic arthritis (pJIA)

Application

- 14.1. The Committee considered the minutes of the Rheumatology Subcommittee of PTAC regarding a clinician's application to fund rituximab (Mabthera) for polyarticular juvenile idiopathic arthritis (pJIA).

Recommendation

- 14.2. The Committee reiterated its previous **recommendation** that the application to fund rituximab (Mabthera) for pJIA in patients who have received inadequate benefit from

tumour necrosis factor (TNF)-alpha inhibitors, or in whom TNF-alpha inhibitors are contraindicated, be declined.

- 14.3. 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

- 14.4. The Committee noted that in February 2014 it had reviewed an application from a clinician to fund rituximab (Mabthera) for the treatment of patients with pJIA unresponsive to adalimumab or etanercept, or in whom the use of tumour necrosis factor (TNF)-alpha inhibitors is contraindicated. PTAC recommended that the application be declined, and further recommended that the applicant resubmit the application clarifying the population being requested for funding, the role of other oral DMARDs prior to initiation of biologics, and considering the appropriateness of tocilizumab funding for this population.
- 14.5. The Committee noted that the Rheumatology Subcommittee of PTAC had reviewed PTAC's minutes at its October 2014 meeting and had responded to the points raised by PTAC. The Subcommittee supported the application and considered that there remained an unmet clinical need in this patient population and requested that PTAC re-review the application. The applicant has advised that they do not have anything further to add (over the Subcommittee's view) at this time.
- 14.6. The Committee noted that the defined population would be patients diagnosed with pJIA who have received insufficient benefit from a community TNF-alpha inhibitor (etanercept and/or adalimumab), prior to which they would have tried methotrexate in combination with either oral or intra-articular corticosteroids as required by the community TNF-alpha inhibitor criteria.
- 14.7. The Committee considered that it was reasonable to accept that there is not much evidence for the use of other disease-modifying antirheumatic agents (DMARDs), although the Committee noted that there appears to be better evidence for leflunomide than rituximab even though leflunomide may not be very effective. Similarly, the Committee agreed that it was unlikely that trials of DMARDs versus rituximab would be available in the near future.
- 14.8. The Committee noted the Subcommittee's comment that most of the patients in the key clinical trial (Alexeeva et al. Clin Rheumatol 2011;30:1163-1172) had polyarticular course JIA at the time of the trial. However, the Committee noted that the majority of patients enrolled in the study were diagnosed with systemic JIA and it was not clear whether, at the time of the trial, the patients had sJIA with poly arthritis or pJIA with polyarthritis.
- 14.9. The Committee noted that there were no new studies supporting the use of rituximab in pJIA since it had last reviewed the application, with the exception of a report of two cases of pJIA successfully treated with rituximab (Berrada et al. Eur J Rheumatol 2014;4:164-6).
- 14.10. The Committee noted a recent publication reporting on adverse events in 348 patients with JIA treated with biologic agents (Tarkaiainen et al. Rheumatology 2014;Dec 10. PMID: 25504896). Of these, a total of 1,516 patient-years were included: 710 on etanercept, 591 on infliximab, 188 on adalimumab, 8 on rituximab, 5 on anakinra, 6 on tocilizumab, 6 on abatacept and 1 on golimumab. The Committee noted that the occurrence for serious infectious adverse events on rituximab (37.5/100 patient-years) was greater than on all other TNF-alpha inhibitors, with a relative risk (RR) of 6.16 (95% CI 1.59, 23.8) (p=0.008).

- 14.11. Overall, the Committee considered that the evidence for rituximab in pJIA was weak and of poor quality. The Committee noted that pJIA is not a registered indication for rituximab and the Committee had significant concerns about the safety of rituximab in this patient group, particularly with respect to the risk of infections.
- 14.12. The Committee agreed with the Subcommittee's view that there was an unmet clinical need in this patient group; however, the Committee considered that it would be more appropriate to review tocilizumab for pJIA given that this was a registered indication for tocilizumab. The Committee noted that the results of the CHERISH trial, a randomised, double-blind withdrawal trial of the efficacy and safety of tocilizumab in polyarticular-course JIA, appeared promising (Brunner et al. *Ann Rheum Dis* 2014; doi: 10.1136/annrheumdis-2014-205351). The Committee considered that PHARMAC staff should approach the supplier of tocilizumab seeking a funding application for tocilizumab in pJIA.
- 14.13. The Committee noted that this is an area of developing research and supported the consideration of rituximab for pJIA on a case-by-case basis under NPPA. However, the Committee noted that named patient applications for rituximab for pJIA in patients who have previously tried TNF-alpha inhibitors cannot generally be considered under NPPA because PTAC has previously considered this patient group, recommended that the funding application be declined, and this group has now been prioritised (ranked) by PHARMAC. The Committee noted that, if tocilizumab was funded for pJIA, patients who had a poor response to tocilizumab could apply under NPPA for rituximab.

15. Tumour Necrosis Factor (TNF)-alpha Inhibitors for undifferentiated spondyloarthritis (u-SpA)

Application

- 15.1. The Committee considered the minutes of the Rheumatology Subcommittee of PTAC regarding a clinician's application to fund tumour necrosis factor (TNF)-alpha inhibitors for undifferentiated spondyloarthritis (u-SpA).

Recommendation

- 15.2. The Committee **recommended** that the funding of TNF-alpha inhibitors (at least one of adalimumab or etanercept) should be widened to include u-SpA, subject to the following Special Authority restrictions, with a medium priority:

Initial application — (undifferentiated peripheral spondyloarthritis) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria: All of the following:

- 1 Patient has undifferentiated peripheral spondyloarthritis with active peripheral joint arthritis in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and
- 2 All of the following:
 - 2.1 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and
 - 2.2 Patient has tried and not responded to at least three months of sulphasalazine at a dose of at least 2 g per day (or maximum tolerated dose); and
 - 2.3 Patient has tried and not responded to at least three months of leflunomide at a dose of up to 20 mg daily (or maximum tolerated dose); and
- 3 Any of the following:
 - 3.1 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
 - 3.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
 - 3.3 ESR and CRP 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 — (undifferentiated peripheral spondyloarthritis) 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 TNF-alpha inhibitor treatment; and
- 2 Either:
 - 2.1 Following 3 to 4 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 The patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to prior TNF-alpha inhibitor treatment in the opinion of the treating physician; and
- 3 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 50 mg every 7 days for etanercept]

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

15.4. The Committee recommended that infliximab not be funded for u-SpA.

15.5. The Decision Criterion particularly relevant to this recommendation is: *(iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

15.6. The Committee noted that in February 2014 it had reviewed an application from a clinician to fund TNF-alpha inhibitors for the treatment of u-SpA. The Committee noted that it had previously recommended that the application be declined. The Committee noted that the supporting publications included in the application (Cruzat et al. *Curr Rheumatol Rep* 2010;12:311-317; 06 De la Mata et al. *Semin Arthritis Rheum* 2011;40:421-9; Kruithof et al. *Arthritis Rheum* 2005;52:3898-3909; Sakellariou et al. *ISRN Rheumatol* 2013:907085; Brandt et al. *J Rheumatol* 2002;29:118-22; Van den Bosch et al. *Ann Rheum Dis* 2000;59:428-433) provided only limited evidence for the use of TNF inhibitors in u-SPA mainly comprising small subgroups of patients enrolled in larger studies, small cohort studies and case reports.

15.7. PTAC had recommended that the application be referred to the Rheumatology Subcommittee for further advice regarding the disease state, the benefits of early TNF treatment in this setting, if there were ways to predict those patients likely to progress and specific Special Authority criteria. The Committee noted that the Rheumatology Subcommittee of PTAC had reviewed PTAC's minutes at its October 2014 meeting.

15.8. The Committee noted the findings from Sampaio-Barros et al. (*J Rheumatol* 2010;37:1195-9) and Collantes et al. (*Joint Bone Spine* 2000;67:516-20) and accepted the Subcommittee's advice that approximately 10%-30% of patients diagnosed with u-SPA would remain undifferentiated in the long term.

15.9. The Committee noted a report of a prospective cohort of 175 spondyloarthritis patients from a single centre, 40 (23%) of whom were classified as u-SpA (Paramarta et al.

Rheumatology 2013;52:1873-8). Patients with u-SpA were younger than patients with ankylosing spondylitis and psoriatic arthritis, with a younger age of disease onset compared to patients with psoriatic arthritis and shorter duration of disease compared with patients with ankylosing spondylitis. Patients with u-SpA tended to have disease severity indexes similar to patients with ankylosing spondylitis, but worse than those with psoriatic arthritis. The Committee agreed with the Subcommittee's advice that the severity of pain and disability experience by patients with severe and intractable u-SPA would be the same or similar to that of patients with ankylosing spondylitis or psoriatic arthritis.

15.10. The Committee noted the findings of several reports it had not reviewed in February 2014:

- Conti et al (Arthritis Rheum 2005;52:1224-6) report on the use of intra-articular infliximab to treat resistant knee monoarthritis in a patient with SpA.
- Dougados et al (Ann Rheum Dis 2010;69:1430-1435) report a 12-week randomised double-blind, placebo-controlled trial of etanercept (50 mg once weekly) vs. placebo in 24 patients with SpA and heel enthesitis proven by MRI and refractory to 3/12 of NSAIDs. Patients needed to have >40 mm of global disease heel activity on a 100mm VAS and be TNF inhibitor naïve on stable medications. The primary efficacy end point was the normalised net incremental area under the curve (AUC) between randomisation and week 12 for the patient's global assessment (PGA) of disease activity (a surrogate end-point). Secondary end points included change from baseline in PGA, heel pain, the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) function subscale, Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and improvement in enthesitis as measured by MRI. Analysis appears to be intention to treat (ITT), although not stated. The mean age of the 24 patients was 37.3 (11.5) years, with a mean of 2.5-3.3 years of heel enthesitis and mean PGA scores of 66.0-72.9 mm, 15/24 (62.5%) had axial involvement and 21/24 (87.5%) had peripheral involvement. Mean normalised net incremental AUC for PGA of disease activity over the 12 weeks was significantly greater in the etanercept: -28.5 vs. -11.1, p=0.029. Significant improvements were also reported in the etanercept vs. placebo group for PGA, -37.6 vs. -11.6, p=0.007; heel pain, -36.7 vs. -13.1, p=0.022; and WOMAC function, -23.2 vs. -7.8, p=0.024. No significant changes were observed in the MRI findings between groups or in the BASDI. One etanercept patient had to withdraw following hospitalisation with tonsillitis and subsequent cellulitis.
- Haibel et al (Arthritis Rheum 2008;58:1981-91) report a 12-week randomised double-blind, placebo-controlled trial of adalimumab (40 mg every other week) vs. placebo in 46 patients with axial SpA without radiographically defined sacroiliitis refractory to NSAIDs, followed by an open label extension to 52 weeks. Patients needed a BASDAI score of ≥ 4 , treatment with prednisone of >7.5 mg/day, DMARDs and other biologics were not permitted. The primary end point was a 40% response according to the improvement criteria of the Assessment of Spondyloarthritis International Society (ASAS 40). Secondary endpoints included BASDAI 50, ASAS 20, SF-36, EQ-5D and ASQoL. Analysis was ITT. The mean age of the 46 participants was 37 & 38 years, with a mean duration of disease of 7 & 8 years, and a mean BASDAI score of 6.3 & 6.7, only one participant had previously been treated with infliximab as part of another study. At week 12, an ASAS 40 response was achieved by 54.5% of the adalimumab-treated patients vs. 12.5% of the placebo-treated patients, p=0.004. At week 12 there were also statistically significant reductions in BASDAI and BASFI scores, and patient and doctor global assessment scores, but not in any of the QoL measures. There were significant improvements in most efficacy end-points at 52 weeks, although this is confounded is obviously biased by the cross-over and open label design. Of note 10 patients who had failed to gain ASAS 40 response had adalimumab dose escalated to 40 mg weekly in the follow-up phase without efficacy response.

- Paramarta et al (Ann Rheum Dis 2013;72:1793-99) reported that 19 out of 40 patients with u-SpA initiated on TNF inhibitors and had ≥ 24 weeks' follow-up. However, outcomes only appeared to be reported for 8 patients. BASDAI scores had statistical improvements between baseline and 24 weeks. However, differences in ASDAS and patient and physician global assessments did not. Of note, length of follow-up was not reported.
- Sieper et al (ABILITY-1, Ann Rheum Dis 2013;7:815-822) report a 12-week randomised double-blind, placebo-controlled trial of adalimumab (40 mg every other week) vs. placebo in 192 biological naïve patients with non-radiographic axial SpA who were intolerant or refractory to NSAIDs, followed by an open label extension of an additional 144 weeks. Patients fulfilled ASAS criteria for axial SpA, had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 , total back pain score of ≥ 4 (10 cm VAS) and inadequate response, intolerance or contraindication to NSAIDs; patients fulfilling modified New York criteria for ankylosing spondylitis were excluded. The primary endpoint was the percentage of patients achieving ASAS 40 at week 12. Secondary end-points included BASDAI, ASDAS, QoL measures and MRI response. Analysis was not ITT, only those who received at least one dose of medication were analysed and seven patients from one site excluded for investigator non-compliance. Patients had a mean age of 38.4 & 37.6 years, with mean BASDAI scores of 6.5 & 6.4, 33/185 (18%) reported were using concomitant DMARDs. At 12 weeks significantly more patients in the adalimumab group achieved ASAS 40 (36% vs 15%, $p < 0.001$). Significant improvements were seen in most other end-points (ASAS responses, ASDAS and BASDAI, QoL). Safety was similar to other adalimumab studies.

- 15.11. The Committee considered that the best evidence was from the two randomised controlled adalimumab trials outlined above (Haibel et al 2008 and Sieper et al 2013), which were of moderate quality.
- 15.12. In light of the advice from the Rheumatology Subcommittee, and the supporting clinical trial evidence that the Committee had not previously reviewed, the Committee considered that its previous recommendation to decline the funding of TNF-alpha inhibitors in u-SpA should be changed to a recommendation to fund TNF-alpha inhibitors in this indication. The Committee noted that although TNF-alpha inhibitors would be unlikely to be particularly cost-effective in this setting, mainly due to their high cost, these agents were already funded for a range of similar conditions where patients have a similar level of disability and lack of alternate treatment options.
- 15.13. The Committee considered that the evidence for etanercept in u-SpA is weak and limited to one small randomised controlled trial (Dougados et al 2010). However, the Committee considered that it was biologically plausible that etanercept would provide similar benefit to adalimumab in u-SpA and it would be reasonable to assume a similar benefit for the purposes of PHARMAC's analyses. The Committee considered that there was no evidence for infliximab in this setting and, therefore, it should not be funded for u-SpA.
- 15.14. The Committee considered that, if TNF-alpha inhibitors were funded for u-SpA, this would be unlikely to result in significant savings from reductions in urgent outpatient clinic attendances (as suggested by the applicant), and the cost of the TNF-alpha inhibitors would be unlikely to be offset by reduced use of other pharmaceutical treatments.
- 15.15. The Committee considered that the applicant's estimate of patient numbers was too low. The Committee noted that the findings of Paramarta et al. (Rheumatology 2013;52:1873-8) would suggest that the number of u-SpA patients would be approximately half the number of ankylosing spondylitis patients with a similar level of disability, which would put the patient numbers at approximately 430 patients per year by about year 5 of funding.

15.16. The Committee considered that the Special Authority criteria proposed by the Rheumatology Subcommittee were appropriate, with the exception of the inclusion of additional joints (subtalar, tarsus, forefoot and sternoclavicular) in the joint count options, which the Committee considered should not be included. The Committee noted the Rheumatology Subcommittee's comment that it would be preferable to include these joints in the currently funded psoriatic arthritis criteria. The Committee noted that increasing the number of potential joints for the joint count criteria would inevitably have the effect of increasing the number of patients who would meet the access criteria, which would have a financial impact that could be significant given the high cost of the treatments. The Committee considered that no convincing evidence had been provided to support the inclusion of the additional joints and did not support this suggested change to the psoriatic arthritis criteria.

16. Tumour Necrosis Factor (TNF)-alpha inhibitors for inflammatory bowel disease-associated arthritis (IBD-A)

Application

16.1. The Committee considered the minutes of the Rheumatology Subcommittee of PTAC regarding a clinician's application to fund tumour necrosis factor (TNF)-alpha inhibitors for inflammatory bowel disease-associated arthritis (IBD-A).

Recommendation

16.2. The Committee **recommended** that the funding of TNF-alpha inhibitors (at least one of adalimumab or infliximab) should be widened to include IBD-A, with a medium priority.

16.3. The Committee **recommended** seeking further advice from the Rheumatology Subcommittee on appropriate Special Authority criteria.

16.4. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

16.5. The Committee **recommended** that etanercept not be funded for IBD-A.

16.6. The Decision Criterion particularly relevant to this recommendation is: *(iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

16.7. The Committee noted that in February 2014 it had reviewed an application from a clinician to fund TNF-alpha inhibitors for the treatment of IBD-A. PTAC recommended that the funding of at least one of adalimumab or infliximab should be widened to include IBD-A with a low priority, and further recommended seeking advice from the Rheumatology Subcommittee on appropriate Special Authority criteria.

16.8. The Committee noted that the Rheumatology Subcommittee of PTAC had reviewed PTAC's minutes at its October 2014 meeting. The Subcommittee recommended two sets of Special Authority criteria (one for IBD-A-axial and one for IBD-A-peripheral) for adalimumab and infliximab in IBD-A and also considered that, in the context of the rheumatology therapeutic area, the priority rating for the funding proposal should be escalated to high. The Subcommittee considered that the overall severity of pain and disability in patients with IBD-A is likely to be worse than patients with IBD alone and worse than patients with ankylosing spondylitis alone, because patients with IBD-A have both gut and joint symptoms that can be problematic.

- 16.9. The Committee noted the Subcommittee's comment that, unlike patients with ankylosing spondylitis or psoriatic arthritis, patients with IBD-A are usually unable to take non-steroidal anti-inflammatory drugs (NSAIDs) as these cause colitis flare. For example, Takeuchi et al reported a relapse rate of from 17% to 28% in a cohort of 209 patients with IBD within 9 days of starting a non-selective NSAID (Takeuchi et al. Clin Gastroenterol Hepatol 2006;4:196-202).
- 16.10. The Committee noted that it had previously reviewed the evidence for TNF-alpha inhibitors in IBD-A. The Committee considered that the evidence was weak and of low quality. The Committee noted that there was a lack of evidence for TNF-alpha inhibitors in IBD-A with ulcerative colitis, and there was a lack of evidence for etanercept in IBD-A.
- 16.11. The Committee considered that, given their high cost and limited evidence of efficacy, the use of TNF-alpha inhibitors in IBD-A was unlikely to be cost-effective relative to other potential funding options. However, the Committee noted that these treatments were already funded for similar disorders with a similar level of disability at a similar point in the treatment course, with similarly poor cost effectiveness. On this basis the Committee considered that its previous priority rating for the funding of adalimumab and infliximab in IBD-A should be raised from low to medium. However, the Committee considered that any criteria for IBD-A would need to be particularly rigorous given the poor quality and incomplete coverage of the evidence versus the currently funded indications.
- 16.12. The Committee considered that, providing the patient group was tightly defined in the access criteria, the number of patients likely to meet IBD-A criteria would be approximately 70 per year.
- 16.13. The Committee reviewed the Subcommittee's proposed criteria for IBD-A–axial. The Committee considered that the proposed criteria were not appropriate as they would allow the use of a TNF-alpha inhibitor as a first-line pharmacologic treatment if sulphasalazine was contraindicated. The Committee considered that advice should be sought from the Rheumatology Subcommittee on potential first-line disease-modifying antirheumatic drugs (DMARDs) that could be reasonably tried prior to a TNF-alpha inhibitor, for example methotrexate. The Committee also requested the Subcommittee's advice on the use of cyclooxygenase-2 (COX-2) inhibitors prior to TNF-alpha inhibitors.
- 16.14. The Committee reviewed the Subcommittee's proposed criteria for IBD-A–peripheral. The Committee considered that the criteria appeared reasonable, with the exception of the Subcommittee's suggested inclusion of additional joints (subtalar, tarsus, forefoot and sternoclavicular) in the joint count options, which the Committee considered should not be included. The Committee considered that this would mean that patients with IBD-A–peripheral would be able to access TNF-alpha inhibitor treatment more readily than the currently funded indications where joint counts are a funding requirement.