

PTAC meeting held on 11 & 12 February 2016

(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. Subcommittee Minutes

Cancer Treatments Subcommittee of PTAC (CaTSoP)

- 1.1. The Committee noted and accepted recommendations related to items 1, 2, 3, 5, 6 and 8.
- 1.2. Regarding item 4, matters arising and correspondence, the Committee noted and agreed with the Subcommittee's recommendation to clarify standard treatments for patients with advanced or metastatic cervical cancer in paragraph 9 of the draft minute from PTAC's August 2015 meeting regarding bevacizumab for first-line treatment of recurrent, persistent or metastatic cervical cancer.
- 1.3. Regarding item 7, bendamustine for CLL and iNHL, the Committee noted that recommendations made by the Subcommittee and by PTAC in their August 2015 meeting minute did not accurately reflect the treatment regimens considered.
- 1.4. The Committee noted that the application by Janssen sought funding for bendamustine:
 - as monotherapy for the treatment of CLL for patients unable to tolerate treatment with FCR
 - in combination with rituximab for the first line treatment of patients with indolent NHL, including mantle cell lymphoma
 - the treatment of patients with relapsed or refractory indolent NHL with or without rituximab
- 1.5. The Committee **recommended** that bendamustine as a monotherapy be funded for the first-line treatment of patients with CLL unable to tolerate treatment with FCR with a medium priority.
- 1.6. The Committee **recommended** that bendamustine in combination with rituximab be funded for the first line treatment of patients with indolent NHL, including mantle cell lymphoma with a low priority.
- 1.7. The Committee reiterated that a recommendation regarding the funding application for bendamustine for the treatment of patients with relapsed refractory indolent non-Hodgkin's lymphoma was deferred pending publication of the HNL 2-2003 study.

Diabetes Subcommittee

- 1.8. The Committee noted and accepted the minutes from the Diabetes Subcommittee meeting of 01 October 2015.

Immunisation Subcommittee

- 1.9. The Committee noted and accepted the minutes from the Immunisation Subcommittee meeting 28 October 2015.

Neurology Subcommittee

- 1.10. The Committee noted the record of the Neurological Subcommittee of PTAC held on 11 November 2015.
- 1.11. The Committee noted and accepted the Subcommittee's recommendation to widen access to lacosamide as a 5th line treatment for refractory epilepsy, and agreed with the Subcommittee that this would have the potential to significantly increase patient numbers and would be a financial risk. The Committee considered that PHARMAC would need to conduct financial analysis to assess the potential impact of widening access.

- 1.12. The Committee noted and accepted the Subcommittee's recommendation that aspirin in chloroform solution remain fully funded on the Pharmaceutical Schedule. The Committee considered that evidence to support the use of aspirin in chloroform solution for the relief of pain due to herpes zoster and post herpetic neuralgia was weak and use of the solution wasn't mentioned in international guidelines. However, the Committee considered the solution was relatively inexpensive and is used by a small number of patients. The Committee noted that transport of chloroform can be problematic for pharmacies.
- 1.13. Regarding item 6 the Committee noted that both the Mental Health Subcommittee and the Neurological Subcommittee had reviewed the funding of methylphenidate for Traumatic Brain Injury (TBI) and Acquired Brain Injury (ABI). The Committee noted and agreed with the Neurological Subcommittee's recommendation that the funding application for methylphenidate for TBI and ABI be declined.
- 1.14. The Committee noted and accepted the remainder of the record of the meeting.

Rheumatology Subcommittee

- 1.15. The Committee noted the record of the Rheumatology Subcommittee of PTAC meeting held on 13 October 2015.
- 1.16. The Committee accepted the recommendations made with the exception of the recommendations made in paragraphs 5.7 and 6.4.
- 1.17. The Committee noted that, in paragraph 5.7, the Subcommittee recommended that PTAC refrain from making funding recommendations for some treatments/indications that would be better considered on a case by case basis through NPPA [Named Patient Pharmaceutical Assessment]. The Committee noted the concerns of the Subcommittee. However, the Committee noted that it was up to PHARMAC to determine what it seeks advice from PTAC on, and the Committee would continue to provide advice and recommendations to PHARMAC on matters referred to the Committee.
- 1.18. The Committee noted that, in paragraph 6.4, the Subcommittee recommended that the Special Authority renewal periods for etanercept (and any other relevant biologic treatment) for all rheumatology indications be increased from 6 to 12 months. The Committee noted that this recommendation would have implications for other indications, in that if this recommendation was progressed it was likely that specialists in other areas e.g. dermatology would request the same change. The Committee considered that because biologic treatments, including TNF inhibitors, are expensive and are among the highest (and fastest growing) expenditure items on the Pharmaceutical Schedule, it was prudent and appropriate for regular 6 monthly review to confirm the treatment is still working. The Committee noted that GPs are able to make renewal Special Authority applications on the recommendation of a relevant specialist, although the Committee acknowledged that not all GPs would have the necessary expertise or willingness to do this. The Committee recommended that the renewal periods be kept at 6 months.
- 1.19. The Committee noted the concerns raised by the Subcommittee in paragraph 4.4 regarding the Trexate brand of methotrexate 2.5 mg tablets being too small and difficult to remove from the blister packs. The Committee requested that this be reviewed by the Tender Medical Evaluation Subcommittee of PTAC, including any complaint letters that PHARMAC has received.

Anti-infective Subcommittee

- 1.20. The Committee noted the record of the Anti-Infective Subcommittee of PTAC meeting held on 4 November 2015.
- 1.21. The Committee noted paragraph 3.7 and considered that the reference to hydrochloric acid is incorrect and that the Anti-infective Subcommittee likely meant to refer to hyperchlorite.

- 1.22. The Committee accepted the recommendations made with the exception of the recommendations made in paragraphs 3.14 and 5.1.
- 1.23. The Committee noted that, in paragraph 3.14, the Anti-Infective Subcommittee recommended that an additional restriction should be added to the listing of moxifloxacin in Part II of Section H of the Pharmaceutical Schedule. The Committee accepted this recommendation, but considered that it would be appropriate to add dermatologists as practitioners who diagnose the identified syndromes. The Committee recommended that the following restriction be added to moxifloxacin on Part II of Section H of the Pharmaceutical Schedule:
- Restricted**
- Post -splenectomy patient with confirmed allergy to penicillin**
- Infectious disease specialist or clinical microbiologist
- All of the following:
1. Patient has had a splenectomy; and
 2. Patient has or Stevens-Johnson syndrome/TEN or confirmed immediate hypersensitivity reaction to penicillin as determined by an immunologist or a dermatologist.
- 1.24. The Committee noted the Subcommittee's discussions in relation to amoxicillin with clavulanic acid granules for oral liquid. The Committee recommended that, should PHARMAC wish to list a 400mg/5mL amoxicillin and 57mg/5mL clavulanic acid formulation, that appropriate investigation including checking that indications for the formulations align be performed prior to listing.
- 1.25. The Committee noted the Anti-Infective Subcommittee's recommendation 5.1, that the application for widening of access for valganciclovir for lung transplant recipients who require prophylaxis to prevent CMV reactivation during steroid pulse therapy be declined. The Committee also noted the Anti-Infective Subcommittee's advice in relation to the use of valganciclovir for the treatment or prophylaxis of Epstein - Barr virus. The Committee noted that this recommendation contradicted a recommendation made by the Transplant Immunosuppressant Subcommittee of PTAC at its May 2015 meeting. The Committee deferred making a recommendation and requested that the evidence in relation to the use of valganciclovir to prevent CMV reactivation during steroid pulse therapy and for the treatment or prophylaxis of Epstein - Barr virus be reviewed again by the Transplant Immunosuppressant Subcommittee, in light of the Anti-Infective Subcommittee's recommendation, prior to PTAC making a recommendation.
- 1.26. The Committee noted the Anti-Infective Subcommittee's recommendation 6.1 in relation to lamivudine prophylaxis for immunocompromised patients. The Committee noted that this recommendation would be an addition to the current Special Authority and that the current Special Authority criteria would remain in place should this recommendation be progressed.

2. Correspondence

Viekira Pak

- 2.1. The Committee noted correspondence from AbbVie Ltd in response to PTAC's August 2015 meeting minutes for paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (Viekira Pak) for the treatment of chronic hepatitis C genotype 1.
- 2.2. The Committee did not consider that this correspondence changed its view and recommendation in relation to paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (Viekira Pak).

Prevenar 13

- 2.3. The Committee noted correspondence from Pfizer New Zealand Limited in response to PTAC's August 2015 meeting minutes for pneumococcal vaccine (Prevenar 13®) for immunisation of adults aged 65 years and over.
- 2.4. The Committee noted the comments from Pfizer regarding the decision criteria (item 18.3). Members noted that relevant consideration was given with regards to the high burden of pneumococcal disease among all Maori and Pacific people, not just those people over 65 years. The Committee noted this is reflected in the minute.
- 2.5. The Committee noted with regards to item 18.11 that Pfizer had included the relevant New Zealand data in the application. Also with regards to item 18.11, the Committee considered the minute should reflect that the CAPiTA study was of high quality; however, was moderately applicable to the relevant population.
- 2.6. The Committee noted with regards to item 18.8 that the minute should reflect there was poor evidence that the SSUAD method had been scrutinised or replicated outside of the study. Members noted 3 of the references included in the Pfizer response were abstracts from a conference that were not published and the additional information provided did not address the Committee's concerns with this assay method.
- 2.7. The Committee thanked Pfizer for its comments and for updating the cost utility analysis.
- 2.8. The Committee considered the information provided does not change its previous recommendation that widening access to Prevenar 13 for vaccination against pneumococcal pneumonia and invasive pneumococcal disease in adults aged 65 years be declined.

Aripiprazole

- 2.9. The Committee noted correspondence from Lundbeck Australia Pty Ltd in response to PTAC's November 2016 meeting minutes for aripiprazole depot injection (Abilify Maintena) for the treatment of schizophrenia.
- 2.10. The Committee noted that two of the trials reviewed, Hough et al. Schizophrenia Res 2010;116:107-17 and the QUALIFY study, were funded by Janssen and Lundbeck, respectively, not Otsuka as stated in the minutes.
- 2.11. The Committee noted that there was a typographical error in the recording of the Kaplan–Meier estimated impending relapse rates in trial 31-07-247 in the minutes, and the difference should have been recorded as (-0.64%, 95% CI -5.26 to 3.99). The Committee agreed that this should be corrected in the minutes.
- 2.12. The Committee acknowledged the feedback from Lundbeck regarding the mixed effect model repeat measurement (MMRM) and the reporting of the intent-to-treat (ITT) analysis in the QUALIFY study.

3. Simeprevir for the treatment of chronic hepatitis C genotype 1

Application

- 3.1. The Committee considered an application from Janssen-Cilag Pty Limited for the funding of simeprevir (Olysio) for the treatment of chronic hepatitis C genotype 1 infection in adults.

Recommendation

- 3.2. The Committee **recommended** that simeprevir (Olysio) should be funded for the treatment of chronic hepatitis C genotype 1 infection if cost-neutral to boceprevir.

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

Discussion

- 3.4. The Committee noted paper: Impact of improved treatment on disease burden of chronic hepatitis C in New Zealand - <https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2014/vol-127-no-1407/6390>, which discusses the issue of burden of hepatitis C disease and the impact of delays in access to treatment.
- 3.5. The Committee noted that simeprevir is a NS3A inhibitor which is indicated for use in the treatment of chronic hepatitis C genotype 1 or 4 infection in combination with other pharmaceutical products for the treatment of chronic hepatitis C infection. The Committee noted that these treatments were either pegylated interferon alfa and ribavirin, or sofosbuvir. The Committee noted that sofosbuvir is not currently publicly funded in New Zealand.
- 3.6. The Committee noted the combined results from the QUEST 1 (Jacobson et al. Lancet 2014; 384: 403–13) and QUEST 2 (Manns et al. Lancet 2014; 384: 414–26) trials which compared the efficacy, tolerability and safety of simeprevir versus placebo as part of a treatment regimen including pegylated interferon alfa and ribavirin in adult treatment-naïve subjects with HCV genotype 1 infection. The Committee noted a sustained virological response 12 weeks following the cessation of treatment (SVR) of 80%. The Committee noted that subjects in these trials had genotype 1 hepatitis C virus (HCV) and were treatment naïve. The Committee noted that variation in SVR response was associated with the presence of the Q80K substitution in those subjects who had HCV subtype 1a. Subtype 1a subjects who did not have a Q80K substitution achieved a SVR more frequently than subtype 1a subjects who did have a Q80K substitution. The Committee noted that the SVR achieved by subjects with HCV subtype 1b did not vary with the presence of the Q80K substitution. The Committee considered that the prevalence of the Q80K substitution was unknown among the New Zealand cohort of people with hepatitis C.
- 3.7. The Committee noted the PROMISE trial (Forns et al. Gastroenterology 2014;146:1669–79) which studied a population that had a relapse of HCV within a year following treatment with pegylated interferon alfa with ribavirin which had resulted in undetectable HCV RNA. Subjects in the experimental arm received simeprevir in combination with pegylated interferon and ribavirin. The Committee noted the SVR of those subjects in the experimental arm was 80%, whereas those who received placebo achieved a SVR of 37%. The Committee noted that the presence of the IL28B genotype, nor the HCV subtype, did not appear to affect the SVR that was achieved. However the presence of the TT allele achieved a SVR of 64% in the experimental arm (19% in the placebo arm) whereas the presence of the CC allele achieved a SVR of 89% (53% in the placebo arm). The Committee noted that subjects with HCV subtype 1a achieved a SVR of 70% in the experimental arm (28% in the placebo arm) and subjects with HCV subtype 1b achieved a SVR of 86% in the experimental arm (43% in the placebo arm).
- 3.8. The Committee noted the results of the PILLAR study (Fried et al. Hepatology 2013;58:1918-29), which aimed to identify the optimal duration and dosage of simeprevir treatment. All patients were treated with simeprevir in combination with pegylated interferon alfa and ribavirin. Subjects were treatment naïve. People who had developed cirrhosis were excluded from the study. The Committee considered that the results of the

PILLAR study did not achieve its aim to definitely identify the optimal dosing and duration of treatment.

- 3.9. The Committee noted the ASPIRE study (Zeuzem et al. *Gastroenterology* 2014;146:430–41) recruited participants that were null responders, partial responders or responders who relapsed after treatment with pegylated interferon alfa with ribavirin. The trial randomised participants to different treatment durations of simeprevir and included a placebo arm. The Committee considered that the results suggested that there was no clear dose response from varying durations of simeprevir treatment although it did suggest that did suggest that 12 weeks treatment was equivalent to 24 or 48 weeks treatment with simeprevir.
- 3.10. The Committee noted the ATTAIN study (Reddy et al. *Lancet Infect Dis* 2015;15; 27–35) which examined simeprevir in combination with pegylated interferon and ribavirin compared to telaprevir in combination with pegylated interferon and ribavirin. The Committee considered that the results suggested that the SVRs obtained from simeprevir and telaprevir treatments are comparable. The Committee reiterated its February 2013 recommendation that it considered telaprevir and boceprevir as being clinically equivalent. The Committee considered that the results suggest that simeprevir does not offer any improvement in SVR over the currently available treatment.
- 3.11. The Committee noted the side effect profile of the simeprevir and the side effect profile of telaprevir. The Committee considered that the results suggested that the overall proportion of participants with side effects observed with simeprevir treatment was less than that observed with telaprevir. The Committee noted the data from the ATTAIN study which suggested that discontinuation of simeprevir or telaprevir treatment occurred in 2% of participants in the simeprevir group compared with 8% in the telaprevir group and anaemia occurred in 13% of the simeprevir group compared with 38% of the telaprevir group. The Committee noted that the level of discontinuation as a result of adverse effects with simeprevir was less than that observed with telaprevir.
- 3.12. The Committee noted the paper: Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET (Gordon et al. *J Hepatol.* 2015;62:286-93) that related to the safety profile in a pragmatic study boceprevir treatment. The Committee noted that serious adverse events were reported in 12% of patients, 66% of patients experienced anaemia, 90% of patients had adverse events that led to a prescription, treatment, or dosage change and 39% of patients discontinued treatment early, most commonly because of adverse events (18%) or lack of efficacy (16%). It noted that hepatic decompensation events occurred in 3% of patients and five deaths occurred and 52% of all patients achieved a sustained virologic response. The Committee noted the declining usage of subsidised boceprevir and considered that this study was consistent with the clinical experience in New Zealand and that this contributed to the declining use of boceprevir in New Zealand.
- 3.13. The Committee noted the COSMOS study (Lawitz et al. *Lancet* 2014; 384: 1756–65) which examined the efficacy and safety of 12 weeks or 24 weeks of simeprevir in combination with sofosbuvir with or without ribavirin. The Committee noted the subjects were HCV genotype 1-infected with compensated liver disease who were prior null responders or HCV treatment-naive subjects. The Committee noted that the SVRs obtained during this study ranged between 93% and 96%. The Committee considered that the SVR was not influenced by the presence or absence of ribavirin. The Committee noted that recent preliminary real-life data from the US showed SVR rates slightly below those in the COSMOS trial in patients with genotype 1 infection (Jensen et al. *Hepatology* 2014;60:219A and Dietrich et al. *Hepatology* 2014;60:220A).
- 3.14. The Committee noted the OPTIMIST-1 trial (Kwo et al. *J Hepatol* 2015;62;s263-s864) which investigated the efficacy and safety of a 8- or 12-week treatment regimen of simeprevir in combination with sofosbuvir in treatment naive and treatment experienced

subjects with chronic genotype 1 HCV infection without cirrhosis. The Committee noted that subjects receiving 12 weeks of simeprevir treatment in combination with sofosbuvir achieved an SVR of greater than 92% irrespective of Q80K polymorphism, IL28B genotype or HCV genotype 1 subtype.

- 3.15. The Committee noted the OPTIMIST-2 trial (Lawitz et al. 50th EASL; 2015. Abstract LP04) which investigated the use of 12 weeks of simeprevir in combination with sofosbuvir in both treatment naïve and experienced people with cirrhosis and HCV genotype 1. The Committee noted that overall reported SVR was 83% with treatment response of 88% for treatment naïve and 79% for treatment experienced people.
- 3.16. The Committee considered that, should simeprevir be funded for use in combination with pegylated interferon and ribavirin, uptake would be similar to that currently seen for boceprevir which has been low. The Committee considered that if patients were in a position to wait for treatment, that they would wait in the hope that interferon-free treatments would become available. The Committee considered that if simeprevir were funded that overall health benefits would be limited because of likely limited uptake of this agent.
- 3.17. The Committee considered that the evidence provided was of good strength and quality and but that the evidence supported the use of simeprevir in HCV genotype 1 only. The Committee noted the prevalence of HCV genotypes in New Zealand and that genotype 1 makes up 57-61% of the cohort. The Committee considered that there would be a need for another agent to treat patients with other genotypes.
- 3.18. The Committee noted that simeprevir should be used with caution in patients with hepatic decompensation and hepatic failure and this is the case when used both in combination with sofosbuvir and with pegylated interferon and ribavirin. Furthermore the Committee noted the hepatitis C virus guidance on testing, managing, and treating hepatitis C from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, which states that simeprevir in combination with pegylated interferon and ribavirin is not a recommended regimen (<http://hcvguidelines.org/full-report/not-recommended-regimens-hcv-treatment>). The Committee considered that there would be a need for another agent to treat patients with severe liver disease.¹

Committee comments in relation to direct-acting antiviral agents for the treatment of chronic hepatitis C

- 3.19. The Committee noted the funding applications and recommendations made to date in relation to the direct-acting antiviral agents (DAAs); sofosbuvir (Sovaldi), ledipasvir with sofosbuvir (Harvoni) and paritaprevir/ritonavir, ombitasvir, dasabuvir +/- ribavirin (Viekira Pak). The Committee considered that there are a number of agents that are also in development which may provide further advantages, such as the ability to treat in all clinical situations without using ribavirin.
- 3.20. The Committee considered that in the setting of the possible availability of a wide variety of other treatments which could treat all HCV genotypes and be used without interferon and/or ribavirin that the place of simeprevir treatment in the medium to long-term is uncertain.
- 3.21. The Committee noted information in relation to the ION trials that investigated the use of ledipasvir with sofosbuvir (Harvoni). The Committee noted that a number of clinical trials had taken place in New Zealand and that a number of patients with difficult clinical situations had been treated via clinical trials. The Committee considered that as a result a

¹ This minute was reviewed by PTAC at its August 2016 meeting. Paragraph 3.18 has been updated to reflect the discussion at the August 2016 meeting (<https://www.pharmac.govt.nz/assets/ptac-minutes-2016-08.pdf>)

substantial proportion of the New Zealand hepatitis C cohort could be treated with 8 weeks of ledipasvir with sofosbuvir rather than 12 weeks.

- 3.22. The Committee considered that commercially, difficulties may arise from procuring agents that had to be used in combination from two different suppliers.
- 3.23. The Committee considered that a number of New Zealand patients are accessing DAAs from overseas which are unregistered for use in New Zealand. The Committee questioned the quality of these medicines and further questioned whether there would be potential issues such as resistance as a result of sub-therapeutic doses of active ingredients in these medications. However the Committee noted that there is no published evidence in relation to this issue.

4. Dornase Alfa for Cystic fibrosis in under 6 year olds

Application

- 4.1. The Committee reviewed an application from PHARMAC to widen access to dornase alfa for patients under the age of 5.

Recommendation

- 4.2. The Committee **recommended** access to dornase alfa be widened to include patients under the age of 5 with a medium priority. This is subject to the following amendments to the Special Authority criteria form used by the Cystic Fibrosis Panel (additions to the criteria proposed by the CF panel in bold; deletions in strike through):

Initial approval criteria for children under the age of 5 to be substantially as follows:

Approvals valid for twelve months for applications meeting the following criteria:

All of the following:

1. Patients must be assessed at regional cystic fibrosis clinics or centers which are under the control of specialist respiratory physicians/pediatricians with experience and expertise in the management of cystic fibrosis and the prescribing of dornase alfa under the Pharmaceutical Schedule is limited to such physicians; and
2. Either:
 - Requiring more than two hospital **respiratory** admissions in a 12 month period; or
 - **Requiring a hospital admission to have a PICC line inserted to manage exacerbations;** or
 - **A chest x-ray showing clear mucus plugging, focal consolidation or a Brasfield score <22/25 done at a time of stability despite currently approved treatment, including repeated physiotherapy assessment and education, and having had at least one admission to hospital; or**
 - **A bronchoscopy done as far as possible at a time of stability which shows significant mucus plugging despite currently approved treatment, including repeated physiotherapy assessment and education, and having had at least one admission to hospital; or**
 - Diagnosis of allergic bronchopulmonary aspergillosis (ABPA); or
 - Undertaking eradication treatment is proposed; and
3. Patient has previously undergone a trial with, or are currently being treated with, hypertonic saline; and
4. All patients having treatment with dornase alfa should be included in the national cystic fibrosis database. Prescribing physicians/pediatricians are required to supply updated patient information on a six monthly basis.

Renewal for dornase alfa for children under the age of 5.

Approvals valid for twelve months for applications meeting the following criteria (additions in bold, deletions in strike through):

All of the following:

1. Patient is compliant with therapy; and
2. In the opinion of the patients treating clinician they believe dornase alfa to be of worthwhile benefit to the patient; **and**
3. Either:
 - Reduction in hospital admissions in the previous ~~6~~12 months; or
 - Reduction in the number of treatment courses of oral antibiotics in the previous ~~6~~12 months; or
 - **Significant improvement in radiological or bronchoscopy findings; or**
 - An eradication of a pathological organism

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

- 4.4. The Committee noted an application arising from a recommendation made by the Respiratory Subcommittee to widen access of dornase alfa for patients under the age of 5 via a Special Authority criteria proposed by the Cystic Fibrosis panel (CF Panel). Members noted that dornase alfa is currently not available as treatment in New Zealand for CF patients under the age of 5. Members noted the minutes from the CF Panel's May 2014 meeting, and the Respiratory Subcommittee's meeting at its March 2015 meeting. Members noted that both the CF panel and the Respiratory Subcommittee had recommended access of dornase alfa be widened to patients under the age of 5. Members also noted that in March 2015 PHARMAC issued a consultation document seeking feedback on amending access criteria for dornase alfa to treat children with CF under the age of 5 years. Members noted that most respondents to the consultation were generally supportive. Members further noted that clinical advice sought from the CF panel on defining the patient group was included in the application. Members also noted that a small number of patients aged under 5 years are currently receiving funded treatment through NPPA.
- 4.5. The Committee noted that cystic fibrosis (CF) is a rare congenital disease that affects about 440 people in New Zealand. Patients with CF lack the enzymes required for normal digestive secretions and for clearing respiratory mucous. Members noted that dornase alfa is a recombinant human deoxyribonuclease enzyme which reduces the viscosity in the lungs, resulting in improved clearance of mucous secretions.
- 4.6. The Committee noted that FEV₁ declines with age in CF patients, and the main objective of management of CF is to maintain growth and prevent or reduce decline in lung function. Members noted that approximately 25% of all CF patients in New Zealand were using dornase alfa, and this uptake was considered low when compared to the US, UK, Australia and Canada (PORT CFNZ National Data Registry, 2013 Registry Report, Cystic Fibrosis Association of New Zealand). The Committee noted advice had been sought from a clinician who specialised in treating CF in New Zealand. This clinician stated that while the PORT CFNZ data is immature from a mortality perspective, the mean FEV₁ in New Zealand adolescent patients appears to decline approximately two years earlier compared with these comparison countries.

4.7. The Committee considered the recommendations given by three guidelines on CF management:

- Royal Brompton Hospital Paediatric Cystic Fibrosis Team; NHS. 2014 guidelines (6th ed) recommend to “consider treating all patients with dornase alfa when they are 6 years old, whatever the lung function”, and to consider preschool children if there is concern over their respiratory status, persistent or recurrent focal x-ray changes, or during an admission for an exacerbation. It also considered that there seemed to be no clinical difference between daily and alternative day treatment for prophylactic use. The authors of the guidelines noted that if there is a response at 3 months to daily treatment, they often switch to alternative day dosing.
- European consensus 2009 (Heijerman, H, et al. Journal of Cystic Fibrosis 2009;8, 295-315) considered that evidence for efficacy in dornase alfa was lacking in patients ≤ 6 years of age, however it was generally agreed that many therapy strategies would have the greatest benefit in infants and young children, before the onset of irreversible disease.
- Cystic Fibrosis Pulmonary Guidelines published by the American Thoracic Society (Flume, et al. Am J Respir Crit Care Med 2007;176:957-969) considered that there were few studies on CF in pre-school children, and that this was due to the difficulty identifying endpoints and barriers in federal regulations that prevent young children being included in studies because of concerns of beneficence.

4.8. The Committee noted limited evidence for efficacy of dornase alfa in this patient group supporting the recommendations from these guidelines. Members considered the following references from the application:

- Byrnes et al. Thorax. 2013;6:643-51 – a New Zealand prospective analysis of respiratory exacerbations, growth and lung function in patients with cystic fibrosis from newborn screening to 5 years of age (n=168). Results showed that participants experience on average 3.66 exacerbations per person-year with 80.1% of patients being community managed and 19.9% requiring hospital admission. Children who received early antibiotic prophylaxis had 26% (95% CI 12% to 38%) lower exacerbation rates compared to children who did not receive 12 months of prophylactic antibiotics. Rates of exacerbations in the first 2 years was associated with reduced FEV₁ Z scores (coefficient -0.20, 95% CI -0.36 to -0.05). Ever having a hospital managed exacerbation was associated with bronchiectasis in chest CT scans (OR 2.67, 95% CI 1.13 to 6.31), and lower weight z scores at 5 years of age (coefficient -0.39, 95% CI -0.74 to -0.05). However, the findings were not significant after adjustment for *Pseudomonas aeruginosa* (*P.aeruginosa*). Members noted the author of this paper is a member of the CF panel.
- NCT00680316 & NCT0017998 – Members noted there were two unpublished RCTs on children under the age of 5 (very small numbers from pilot studies); however, no results have been published to date.
- Berge et al. J of CF 2003;2:183-8 – a pilot study that reported patients aged 2 years or less who were treated with dornase alfa for 2 or 4 weeks of dornase alfa treatment resulted in improved V_{maxFRC} by 72 mL/s (95% CI 38-107 mL/s, p=0.002).
- McKenzie et al. Paed Pulmonology. 2007;42:928-37 – a company-sponsored post-registration prospective observational study post closure of the Epidemiologic Registry of Cystic Fibrosis (ERCF) study which consisted of 15,979 CF patients. Sub-analysis showed that 3,486 of patients enrolled in the ERCF study were under 5 years of age. The study reported 328 out of 3486 (9.4%) received dornase alfa prior to their fifth birthday for a total of 267.93 patient years – this was on average less than one year per patient. The study reported that 0.18% of serious adverse events (SAEs) were

classified as “possibly related to dornase”, with the most frequently reported one being haemoptysis. Results also showed patients prescribed dornase alfa were likely to be sicker and older, but SAEs were not common for patients under 5 years of age thus confounding interpretation of data to younger patients.

- Hodson et al. Paed Pulmonol 2003;36:427-32 - an analysis using the same observational data as McKenzie et al. 2007. It reported a reduced FEV₁ by 2.3% in untreated patients compared to a 0.3% improvement in treated patients with dornase alfa, that is, a treatment benefit of 2.5% (95% CI 0.7-4.4%). Treated patients were also reported to have a significant reduction in exacerbation frequency – 25 fewer exacerbations per 100 treated patients per year (95% CI -0.12 to -0.39) – and this effect was more significant in younger patients 6-13 years of age.
 - Padman et al. J of CF 2008;7:385-90 - a retrospective cohort study on registry data from three US CF centres. One of the three centres used dornase alfa 82% of the time in infants < 2 years of age compared to 10% in the remaining two centres, and fewer supplemental feeds (56% vs. 78% (p = 0.04)). It was reported that dornase alfa use prior to two years of age was associated with average BMI percentiles 10.2% higher at ages 2-3 compared to non-treated patients. However, dornase alfa use was associated with an increased risk of developing *P. aeruginosa* infection at an earlier age (2.3 years vs. 3.6 year p=0.03).
- 4.9. The Committee considered that although the evidence base was poor, it was biologically and physiologically plausible that earlier treatment with dornase alfa could result in better health outcomes in later years in children under the age of 5 years.
- 4.10. The Committee considered that dornase alfa would be used in combination with digestive enzyme replacement, vitamin supplementation, hypertonic saline and salbutamol. It was noted that the use of nutritional support and antibiotics (oral, nebulised and parental) may decrease. Members noted that funded access to systemic enzyme replacement therapy was not currently available. Members considered that children would most likely take a total dose of dornase alfa similar to adults.
- 4.11. The Committee noted that current literature noted risks associated with dornase alfa treatment could include haemoptysis and increased risk of *P. aeruginosa* infection for this patient group. Members also noted an FDA label which suggested younger patients had increased cough (45%), rhinitis (35%) and rash (6%).
- 4.12. The Committee noted there is an unmet clinical need in the young CF population who needed treatment to prevent early decline in lung function and colonisation which establishes a trajectory towards poorer functions later in life. Members noted that Māori and Pacific patients had a lower prevalence and incidence of CF compared to New Zealanders of European descent.
- 4.13. The Committee considered that the proposed criteria would increase the number of new patients to treatment, and that PHARMAC’s estimated patient prevalence numbers of 12 patients per year appeared to be appropriate. Members considered that under the proposed criteria, not all patients under the age of 5 would access or tolerate dornase alfa treatment; however, restriction criteria should be placed on dornase alfa to manage fiscal risk.
- 4.14. The Committee noted that there was uncertainty whether early treatment with dornase alfa would reduce hospital admissions in subsequent years. Members noted a small data set provided by PHARMAC suggesting that admissions occur more frequently in younger children. Members however also noted that results from Byrnes et al. Thorax. 2013;6:643-51 reported the converse, in that there was an increased exacerbation rate of 9% per year of age (95% CI 4% to 14% p<0.001).

- 4.15. The Committee agreed with the CF panel's recommendation that initial and renewal criteria should be for 12 months instead of 6 months for this patient group. Members considered the hospital admission criteria should be limited to two hospital respiratory related admissions, or one hospital admission for patients that require a peripherally inserted central catheter (PICC) for intravenous antibiotic courses to manage respiratory exacerbations. Members considered only one hospital admission should be required if there was evidence of confirmed mucus plugging during a time of stability., Members considered investigations of mucus plugging should include chest x-ray, Brasfield score of <22/25, or bronchoscopy conducted during a time of stability. Members also considered patients should be under concomitant physiotherapy and be provided educational support.
- 4.16. The Committee considered the proposed renewal criteria of reduction in hospital admissions; or reduction in number treatment courses of oral antibiotics during a time-period prior to renewal period should be 12 months, were appropriate. Members also considered an improvement in disease should be by evidence from radiological or bronchoscopy findings.
- 4.17. The Committee considered that patients should be allowed to continue treatment until they can undergo spirometry, which is typically not possible for children under 5, and that at this stage the use of dornase alfa should be reconsidered by the CF panel with respect to the likelihood of ongoing benefit and in a way that was consistent with the current access criteria. Members considered that in practice this could be stressful for patients and their families if they were required to stop treatment for a period of months. Members noted this transition period where patients may be ineligible for dornase alfa, based on their clinical assessment not meeting current access criteria. Members considered that continuation of treatment should be determined by the Cystic Fibrosis panel.
- 4.18. The Committee noted the lack of robust data in children under 5 created significant uncertainty in the treatment benefit and risks. However, on balance, the Committee was supportive of widening access to children under the age of 5 due to high health need. Members considered that further research should be conducted on this patient group to address these issues from the data be collected in the national CF database in patients receiving dornase alfa.

5. Zoster Vaccine

Application

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

Recommendation

- 5.2. The Committee **recommended** zoster vaccination be listed on the Pharmaceutical schedule for vaccination of people aged 65 with a 2 year catch-up programme for people aged between 65 and 80 years with a low priority.
- 5.3. The Committee **recommended** zoster vaccination be listed on the Pharmaceutical schedule for vaccination of people aged 65 with no catch up programme with a medium priority.
- 5.4. 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 5.5. The Committee noted that it had reviewed zoster vaccination previously at its August 2014 and 2015 meetings and had recommended zoster vaccine be listed on the Pharmaceutical Schedule with a medium priority. The Committee noted it previously recommended the catch-up programme should allow for all people over the age of 65 years the opportunity to receive one dose of zoster vaccine, but that the time period for the catch-up programme should be limited to two years. The Committee noted it also recommended PHARMAC staff review their cost utility modelling to confirm whether 65 years remains the most cost efficient age to vaccinate.
- 5.6. The Committee noted the updated CUA information prepared by PHARMAC staff. Members noted PHARMAC modelled a 2-year catch-up programme for all people over the age of 65 years and an on-going catch-up programme for people at age 75 years. Members noted that Australia had recently made a decision to fund the zoster vaccine for people aged 70 years with a 5-year catch-up programme for people aged 71-79 years from 1 November 2016.
- 5.7. The Committee noted the assumptions in the CUA model and considered the modelling should better account for the relationship between increasing age and increased morbidity from herpes zoster and post herpetic neuralgia (PHN). Members also noted increased age is an important risk factor for PHN (Jung et al. Neurology 2004;62:1545-1551) and that modelling to date has a fixed vaccine efficacy against PHN at all ages conditional on the incidence of zoster infection. Members noted the model includes PHN, but does not capture morbidity from other impacts of the disease. Members considered that the vaccine is less likely to be effective in older people, however if it is effective then older people are likely to receive greater absolute health benefit from the vaccine (because of the dominance of higher case morbidity with age).
- 5.8. The Committee noted evidence that there is a decreased Quality of Life with PHN with advancing age and considered that this has been reflected in the modelling.
- 5.9. The Committee reiterated that it considered 65 was a reasonable age as that coincided with influenza vaccination however it is important to note that the vaccine efficacy decreases markedly with age.
- 5.10. The Committee considered that determining the optimal age(s) of vaccination and catch-up programmes is largely a financial decision that has to take into account budget impact and the cost utility analysis. Members noted the significant budget impact of a broad catch-up programme and that it may be unlikely to be affordable due to the poorer cost effectiveness and high cost of the vaccine. The Committee considered that a 2-year catch-up programme for all patients over the age of 65 would be appropriate but would be a lower priority than funding the vaccine for people aged 65 with no catch-up programme, because of these factors.

6. Ipilimumab for previously treated and unresectable stage IIIc or IV melanoma

Application

- 6.1. The Committee considered the application from Bristol Myers Squibb (NZ) Limited, for the funding of ipilimumab (Yervoy) for the treatment of patients with previously treated unresectable stage IIIc or IV melanoma. This included the recently published long term follow up survival data from the pivotal randomized study.

Recommendation

- 6.2. The Committee **recommended** that ipilimumab be funded with a low priority for the treatment of patients with previously treated unresectable stage IIIc or IV melanoma

- 6.3. The Decision Criteria particularly relevant to this recommendation are (i) *The health needs of all eligible people in 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 it had previously considered the funding of ipilimumab at its February 2014 and August 2012 meetings where it recommended that the application be declined because the evidence for long term overall survival was of poor quality and there remained uncertainty of the magnitude of benefit from ipilimumab. The Committee noted that the application should be reviewed once longer term follow up from the randomized study was available. Members noted that the Cancer Treatments Subcommittee considered the application at its October 2012 meeting where it recommended the application be declined because the evidence for any long term benefit was weak.
- 6.5. The Committee noted evidence from a pooled analysis of long term follow up of ipilimumab pre-treated advanced melanoma patients from the phase II and III studies was previously considered at its February 2014 meeting and has now been published as Schadendorf et al. (JCO 2015; 33;1-7). Members noted that this analysis suggested a plateau at 21% in the survival curve beginning around 3 years after randomisation.
- 6.6. The Committee reviewed long term overall survival evidence published by Maio et al. (JCO 2015;33:1191-9) which reports the five year survival rates for treatment naïve patients with advanced melanoma who received ipilimumab in the phase III randomized trial reported by Robert et al. 2011 (NEJM 2011; 364:2517-26).
- 6.7. The Committee noted that 17.2% of patients in the ipilimumab-dacarbazine arm and 21% of patients in the placebo –dacarbazine arm with stable disease or better from week 12 through week 24 without dose limiting toxicities received at least one maintenance dose and eleven patients in each arm received maintenance treatment for more than 2 years. Members also noted that of the 502 patients were randomized to receive treatment, there were 199 deaths in the ipilimumab-dacarbazine arm compared to 227 deaths in the placebo-dacarbazine arm.
- 6.8. The Committee noted that median overall survival (OS) was 11.2 months (95% confidence interval (CI) 9.5-13.8) in the ipilimumab-dacarbazine arm compared to 9.1 months (95% CI, 7.8-10.5) in the placebo-dacarbazine arm.
- 6.9. The Committee noted that at a minimum follow up of 5 years, 18.2% of patients in the ipilimumab-dacarbazine treatment arm were still alive at 5 years compared to 8.8% of patients in the placebo-dacarbazine arm and therefore a 9.6% long term survival gain. Members considered the survival curve shows a similar plateau around 3 years after randomisation as seen in the data from Schadendorf et al.
- 6.10. Members noted that among patients who survived at least 5 years, 30% of patients in the ipilimumab-dacarbazine arm and 55% of patients in the placebo-dacarbazine arm received at least one other subsequent treatment and that the majority of this was due to disease progression.
- 6.11. The Committee considered that Maio et al. provides relatively strong evidence that ipilimumab provides a long term survival difference and addresses previous concerns

regarding the magnitude of benefit provided by ipilimumab for patients with advanced melanoma.

- 6.12. The Committee noted that issues remained with regards to ipilimumab related adverse events and toxicity, however, considered that these were well known within the clinical community and not of sufficient significance to outweigh the long term survival benefits.
- 6.13. The Committee considered that the pricing being sought by the supplier was high and was adversely affecting its cost-effectiveness and that the priority recommendation would improve with lower pricing.
- 6.14. The Committee noted that evidence was now emerging for the use of ipilimumab in combination with PD1 inhibitors and, while the data had not been considered by the Committee and appeared to still be immature in comparison to the overall survival data available for ipilimumab monotherapy, it indicated potential future treatment paradigms for advanced melanoma.

7. Pembrolizumab Economic Analysis

Application

- 7.1. The Committee considered a request from PHARMAC staff seeking feedback regarding the economic analysis for pembrolizumab (Keytruda, Merck Sharpe & Dohme) as monotherapy for the treatment of patients with metastatic or unresectable melanoma stage III or IV as detailed in Technology Assessment Report (TAR) No 271.

Discussion

- 7.2. The Committee noted that the application from Merck Sharpe & Dohme (MSD) for the funding of pembrolizumab (Keytruda) for the treatment of patients with metastatic or unresectable melanoma stage III or IV had been considered by PTAC at its November 2015 meeting and recommended it be funded with low priority. The Committee also noted the application had been considered by the Cancer Treatments Subcommittee at their meeting in September 2015 where it recommended funding with a low priority.
- 7.3. The Committee noted that evidence from Keynote-006 (Robert et al. NEJM 2015;372:2521-32) which was considered at its meeting in November 2015. The Committee noted that unpublished data from this study at a median follow-up of 13.8 months had been presented at the Society for Melanoma Research November 2015 meeting. Median 12 month progression free survival (PFS) was 37.7% and 36.3% in the two-weekly and three-weekly pembrolizumab arms respectively compared with 17.2% for the ipilimumab arm, with corresponding hazard ratios of 0.60 (95% confidence interval (CI), 0.49-0.74) and 0.59 (95% CI, 0.48-0.73) respectively. Members noted that the published HR value was 0.58 (Robert et al. NEJM 2015).
- 7.4. The Committee noted that key inputs to the analysis included overall survival and PFS for pembrolizumab derived from KEYNOTE-066 (Robert et al. 2015) and an indirect comparison with dacarbazine using evidence from the trial reported in Robert et al. 2011. The Committee considered that indirect comparisons are inherently problematic. However, the Committee considered the method of indirect comparison detailed in TAR No.271 and in particular comparison of the product of hazard ratios was reasonable.
- 7.5. The Committee considered the method used to estimate the number of patients with metastatic or unresectable stage III or IV melanoma and the utility values for health states were reasonable. However, members noted that the analysis accounted for a group of patients currently diagnosed with advanced melanoma which was about 20% of the estimated number of first year patients with stage III or IV advanced melanoma, and considered that this figure may be an underestimate and in reality could be larger and as much as 100% in year one. Members further noted that there may be an additional 10%

of current long-term survivors which should be included in the numerical patient estimate analysis.

- 7.6. The Committee noted that analysis did not include the impact of clinically significant adverse events (AE) including immune effects. Members considered that AEs were difficult to quantify for patients with advanced melanoma as they varied widely, and, due to the current short length of follow up data available to date from the studies, the durations to which AE effects persist were uncertain. However, the Committee considered that for a disease with fatal outcomes that if clinically meaningful AEs from treatment were to be included in the economic analysis they would have a small overall impact, which was unlikely to be meaningful when compared with the treatment effect size, and therefore considered the analysis appropriate.
- 7.7. Members noted that the proposed Special Authority criteria specified a 3 month (13 week) approval period and considered that, under this criterion, patients may be able to receive up to 5 three-weekly cycles of treatment within an approval period of this duration. Members noted that in the pembrolizumab clinical trials tumour response was assessed at 12 weeks, upon completion of the fourth cycle. Members considered if treatment were to be restricted to only 4 cycles for patients who do not respond to pembrolizumab then in practice response assessment would need to be undertaken prior to week 12.
- 7.8. Members noted that the proportion of patients who would respond to pembrolizumab treatment is based on the KM curve for PFS from Keynote-006 (Robert et al. 2015) which reported around 60% PFS at 13 weeks based on Integrated Radiology and Oncology Assessment (IRO). However, members considered that the investigator assessment result would be more comparable to clinical practice outside of the strict assessment conducted in a trial environment and therefore that at least 70% of patients after the initial 13 weeks of treatment would be judged by their treating clinicians as responding to treatment, who would then apply for ongoing funding for their patients. Members also considered that the proportion of patients remaining on treatment beyond 26 weeks would likely have similar survival patterns to those reported by published data.

8. PD-1 Inhibitors

Application

- 8.1. The Committee considered a supplementary paper from PHARMAC staff regarding PD-1 inhibitors for the treatment of melanoma and other cancers.

Discussion

- 8.2. The Committee noted that the programmed death 1 protein (PD-1) receptor expressed on activated T-cells is engaged by the tumour-expressed ligands PD-L1 and PD-L2 to inhibit T-cell activation and promote tumour immune escape. The Committee noted that PD-1 inhibitors, such as pembrolizumab (Keytruda, Merck Sharpe & Dohme) and nivolumab (Opdivo, Bristol-Myers Squibb) disrupt PD-1 mediated signalling and may restore anti-tumour immunity.
- 8.3. The Committee noted that there are ongoing clinical trials investigating a number of PD-1 inhibitors for the treatment of a large variety of different cancer types. The Committee noted that the PD-1 inhibitors at the most advanced stages of clinical trials are pembrolizumab and nivolumab, both of which have been brought to market internationally.

Pembrolizumab

- 8.4. The Committee noted an application from Merck Sharpe & Dohme for the funding of pembrolizumab for the treatment of metastatic or unresectable melanoma stage III or IV

had been considered at their meeting in November 2015 where funding was recommended with low priority.

- 8.5. The Committee also noted the application had been considered by the Cancer Treatments Subcommittee at their meeting in September 2015 where it recommended funding with a low priority.
- 8.6. The Committee noted that PTAC had previously reviewed evidence for the use of pembrolizumab in the treatment of advanced melanoma from the following studies:
- KEYNOTE-001 (Hamid et al. N Engl J Med 2013;369:134-44) an open label multicenter, phase 1 dose escalation study in patients with locally advanced or metastatic melanoma or non-small cell lung cancer.
 - KEYNOTE-002 (Ribas et al. Lancet Oncol 2015;16:908-18) a randomized phase II study comparing two dosing regimens of pembrolizumab (2mg/kg or 10mg/kg) given every three weeks with investigator-choice chemotherapy in patients with advanced melanoma refractory to prior treatment with ipilimumab and, if BRAF V600 mutant-positive, refractory to previous treatment with a BRAF or MEK inhibitor or both.
 - KEYNOTE-006 (Robert et al. N Engl J Med 2015;372:2521-32) a randomized, controlled, phase III study of pembrolizumab given at 10mg/kg every 2 weeks or every 3 weeks.
- 8.7. The Committee noted longer term follow-up from KEYNOTE-006 at a median follow-up of 13.8 months was recently presented at the Society for Melanoma Research (SMR) 2015 International Congress which reported PFS rates in pembrolizumab at 12 months were 37.7% in the 2-weekly arm, 36.3% in the 3-weekly arm compared to 17.2% in the ipilimumab arm (HR 0.60, 95% CI 0.49-0.74, $p < 0.00001$ and HR 0.59, 95% CI 0.48-0.73, respectively). ORR was 36.2% and 36.1% in the pembrolizumab 2-weekly and 3-weekly arms respectively (95% CI 0.48-0.73) compared to 12.9% for the ipilimumab arm (95% CI 9.2-17.5).
- 8.8. The Committee noted there are studies underway investigating the use of pembrolizumab in combination with ipilimumab (an immunotherapy that regulates T-cell activation via inhibition of cytotoxic T-lymphocyte antigen 4 (CTLA-4)) and other immunotherapies, epecadostat and T-VEC, in patients with advanced melanoma. The Committee also noted there are a number of mostly phase I studies of pembrolizumab for the treatment of other cancers including breast, head and neck, gastric, and haematologic malignancies.

Nivolumab

- 8.9. The Committee noted that a funding application for nivolumab had not yet been considered by PTAC or CaTSoP. The Committee also noted that PHARMAC had recently received applications from Bristol-Myers Squibb for the funding of nivolumab, as monotherapy and in combination with ipilimumab, for the treatment of metastatic melanoma and as monotherapy for the treatment of locally advanced non-small cell lung cancer.
- 8.10. The Committee noted that the key evidence for the use of nivolumab comes from CHECKMATE-066 - a randomised, controlled, double-blind, phase III study of nivolumab compared with dacarbazine in previously untreated patients who had metastatic melanoma without a BRAF mutation (Robert et al. N Engl J Med 2015;372:320-30).
- 8.11. The Committee noted Robert et al 2015 reported that at one year, the OS rate was 72.9% (95% CI 65.5-78.9) in the nivolumab group compared to 42.1% (95% CI 33.0-50.9) in the dacarbazine group (HR 0.42, 99.79% CI 0.25-0.73, $p < 0.001$). The median PFS was 5.1

months versus 2.2 months respectively (HR 0.43, 95% CI 0.34-0.56, $p < 0.001$). The ORR was 40.0% (95% CI 33.3-47.0) for the nivolumab group compared to 13.9% (95% CI 9.5-19.4) in the dacarbazine group (OR 4.06, $p < 0.001$). Drug related adverse events of grade 3 or 4 occurred in 11.7% and 17.6% respectively.

- 8.12. The Committee noted that longer term follow-up from CHECKMATE-066 at a median follow-up of 18.5 months was recently presented at the Society for Melanoma Research (SMR) 2015 International Congress which reported the median OS was not reached in the nivolumab arm and was 11.2 months in the dacarbazine group. (Atkinson et al. SMR 2015 poster).
- 8.13. The Committee noted that trials were also being undertaken to assess the efficacy of nivolumab in combination with ipilimumab (CHECKMATE-037 Weber et al., CHECKMATE-067 Larkin et al., and CHECKMATE-069 Postow et al.)
- 8.14. The Committee noted that longer term follow up, median 32.7 months, from this study was presented at the SMR 2015 International Congress which reported the 3 year OS rate was 68% in patients treated with combination nivolumab and ipilimumab.
- 8.15. The Committee noted that all the currently available data for PD-1 inhibitors for the treatment of advanced melanoma was relatively immature but considered that from the information provided, the highest strength and quality evidence appeared to be for the use of nivolumab as monotherapy from CHECKMATE-066 for which abstract data is available to 2 years with limited censoring.
- 8.16. The Committee noted there appears to be no head-to-head trial data of pembrolizumab compared to nivolumab and considered that, in the absence of head-to-head data, the best method for comparing these agents was by comparison of the published data for overall survival from CHECKMATE-066 and KEYNOTE-006. The Committee considered that there were limitations with this type of comparison in particular due to data immaturity. However, the comparison indicated that nivolumab and pembrolizumab may have a similar therapeutic effect.
- 8.17. The Committee noted that from the available published data it was not possible to produce an overall survival curve for nivolumab in combination with ipilimumab as OS data would not be available until the end of 2016. The Committee considered that based on the published PFS data from 067 and 069 there appears to be benefit from the addition of ipilimumab over monotherapy but was associated with more toxicity, the effects of which appear to persist even once ipilimumab treatment has ceased.
- 8.18. The Committee noted that recently published Phase III study data for nivolumab for the treatment of NSCLC and RCC was immature but appeared promising.
- 8.19. The Committee noted that the literature was not resolved regarding the use of PDL1 expression as a potential biomarker for targeting treatment. However, the literature appeared to indicate there may be a superior effect in tumours with strong expression. Members considered that further research would be helpful in determining the use of biomarkers to target patient populations that would most benefit from treatment with PD-1 inhibitors.
- 8.20. The Committee considered that advice should be sought from the Cancer Treatments Subcommittee regarding PD-1 inhibitors and the framework for their analysis.

9. Rituximab subcutaneous preparation for Non-Hodgkin's Lymphoma (NHL)

Application

- 9.1. The Committee considered the application from Roche (NZ) for the funding of rituximab (MabThera) subcutaneous for the treatment of patients with non-Hodgkin's lymphoma.

Recommendation

- 9.2. The Committee **recommended** that the application from Roche Products NZ for the funding of rituximab (MabThera) subcutaneous for the treatment of patients with non-Hodgkin's lymphoma be declined.
- 9.3. The Decision Criteria particularly relevant to this recommendation are: *(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

- 9.4. The Committee noted that the intravenous (IV) formulation of rituximab is currently funded for patients with a variety of indications and is generally administered at a dose of 375mg/m² Body Surface Area (BSA). The Committee noted that the subcutaneous (SC) formulation of rituximab is given as a fixed dose of 1400mg irrespective of patients BSA.
- 9.5. The Committee noted that rituximab SC is indicated only for the treatment of patients with NHL, with the datasheet specifying the same NHL patient groups as the rituximab IV datasheet. Members noted that rituximab SC is currently being investigated for the treatment of patients with chronic lymphocytic leukaemia.
- 9.6. The Committee noted that SC administration requires delivery of relatively large volumes which is made possible as rituximab SC is concentrated at 120mg/ml (compared to 10mg/ml for the IV formulation) and the addition of recombinant hyaluronidase, an enzyme used to increase the dispersion and absorption of co-administered chemicals.
- 9.7. The Committee noted that small molecule oncology drugs typically have a narrow therapeutic window and dosage is based on body size to minimise inter-patient pharmacokinetic variability. The Committee noted that the dosing of monoclonal antibody therapy (MABs) have followed the same paradigm. The Committee considered it likely that MABs have different distribution and elimination mechanisms in comparison to small molecule treatments and that clinical practice may move away from BSA proportional dosing of MABs in future.

SPARKTHERA

- 9.8. The Committee noted evidence for the pharmacokinetics and safety of rituximab SC from the 'SparkThera' study - a two-stage randomised, open-label Phase 1b study in patients receiving maintenance therapy for follicular lymphoma (Salar et al. JCO 2014;32:1782-91). The Committee noted that in stage one, patients who responded to rituximab induction were randomised to rituximab SC at a dose of 375 mg/m² (n=34), 625 mg/m² (n=34), or 800 mg/m² (n=40) or rituximab IV at a dose of 375 mg/m² (n=16). The Committee noted that pharmacokinetic modelling of stage one data predicted a fixed SC dose of 1400mg/m² would yield a rituximab serum trough concentration (C_{trough}) in the same range as rituximab IV irrespective of BSA and dosing interval with comparable safety profile. Members noted that study participants had an average BSA of 1.9 m² (1.4-2.5).
- 9.9. Members considered it was unclear what pharmacokinetic parameter relates to clinical efficacy but noted that the authors state C_{trough} had been selected as the primary pharmacokinetic parameter as it was considered to reflect the degree of target-site saturation during the entire dosing interval.
- 9.10. The Committee noted that in stage two, patients were randomised to rituximab SC 1400mg/m² (n=77) or rituximab IV 375 mg/m² (n=77) given as maintenance treatment at

two or three month intervals with the objective of demonstrating non-inferior rituximab SC C_{trough} compared to the IV formulation. The Committee noted the geometric mean C_{trough} ratio, the primary endpoints, were 1.24 (90% CI, 1.02-1.51) and 1.12 (90% CI, 0.86-1.45) for the two monthly and three monthly regimens respectively.

SABRINA

- 9.11. The Committee noted evidence from the SABRINA study - a two-stage, randomised, controlled, open-label phase III study in patients with previously untreated CD20 positive grade 1-3a follicular lymphoma (Davies et al. Lancet Oncol 2014;15:343-52). The Committee noted that patients were randomly assigned to receive rituximab IV 375mg/m² (n=54) or fixed dose SC rituximab 1400 mg (n=64) every three weeks. The Committee noted that the geometric mean C_{trough} ratio at cycle 7, the primary endpoint, was 1.62 (90%CI 1.36-1.94) in the per protocol population.
- 9.12. The Committee noted that patients with a complete or partial response following induction therapy in part one continued with SC rituximab or IV rituximab every 8 weeks for 2 years along with an additional 283 patients with follicular lymphoma recruited into in stage two of the SABRINA study. The Committee noted the stage two data has not yet been published but had been provided by the applicant. The Committee noted that in the pooled analysis (stage 1 and 2) overall response rate (ORR) during induction, the primary outcome for this part of the study, was 84.4% (95% CI, 78.7-89.1) in the IV group compared to 83.4% (95% CI, 77.6-88.2) in the SC group. Members noted that the proportion of patients with grade 3 or worse adverse events (AEs) was comparable between groups and the number of treatment-related AEs was higher in the SC group due to a higher rate of mainly grade 1 or 2 administration AEs.
- 9.13. Members noted that during the study three participants received a higher than intended dose when administered SC solution intravenously (in combination with the IV formulation) and one participant received the IV dose administered via SC route resulting in under dosing. Members noted that no AEs were reported but considered that these errors highlight potential safety issues of having two formulations in use within the same patient population.
- 9.14. The Committee noted the 410 study participants had a mean BSA of 1.83 m² but that the mean and median values differed slightly between the arms. Members considered this was likely due to the uneven gender distribution between the groups (mean BSA 1.81 for the SC group, 48% female and 1.86 for the IV group, 58% female).

PREFAB

- 9.15. The Committee noted that patient preference for IV or SC rituximab given in combination with chemotherapy was investigated in the 'PrefMab' study - a phase IIIb, prospective, multicentre, multi-national, open-label randomised study (Rummel et al. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Congress 2015 Poster and Abstract PCN219). The Committee noted the primary endpoint was dosing route preference, assessed via a Patient Preference Questionnaire, post-rituximab therapy in cycles 6 and 8. The Committee noted that patient satisfaction was reported to be greater in 4 of 5 domains but as no statistical measurements were presented the significance of this result was unclear. Members noted that 70% of the arm B cohort were on a 6 cycle chemotherapy regimen and this cohort appears to report increased satisfaction with the post-8-cycle assessment. Members considered this appeared to suggest a correlation between increased satisfaction with SC rituximab when not co-administered with IV chemotherapy regimens, however, noted that this effect is not evident in final data for all groups where 43% of patients received 8 week chemotherapy regimens.

- 9.16. The Committee also noted a time in motion study conducted in three UK centres conducted alongside a phase III trial of SC rituximab in patients with NHL (Rule et al. J Med Econ 2014;1-10). The Committee noted that the study reported savings in health professional and patient time in terms of preparation and administration of IV and SC rituximab. Members noted that in this study IV treatment was given as monotherapy while data was collected for SC rituximab when administered concurrently with chemotherapy regime. Members noted that the protocols used in this study were unclear and so considered it was also unclear if this study would be applicable in a New Zealand setting.

SUMMARY

- 9.17. The Committee considered that the evidence provided by the supplier in support of this application to be of high strength and moderate quality. Members noted that the supplier had provided open label studies, including a reasonably large pharmacokinetics study but a relatively small clinical efficacy study. Members considered that larger studies were needed to determine if there was any clinically significant difference in treatment efficacy between the doses. The Committee considered that overall the clinical benefit of the SC over the IV presentation was unclear.
- 9.18. The Committee considered that if there were advantages from use of the SC formulation these would be heavily dependent on treatment protocols, duration of infusion, staffing levels and compounding costs which likely vary between treatment centres. Members also noted that the advantage for patients receiving rituximab in combination with IV chemotherapy regimens was uncertain and the risk of administration error if both IV and SC products were in use.
- 9.19. The Committee noted that the application should be considered in the context of future biosimilar competition and noted that the introduction of SC rituximab may fragment the market and potentially reduce savings from a competitive process. The Committee noted that in order to establish tolerability the first dose of rituximab, administered by IV, would likely need to be the same brand as the SC formulation. Members considered this may result in three different rituximab products on the market which would be an undesirable situation both in terms of cost and patient safety.

10. Bevacizumab for treatment of patients with relapsed or recurrent glioblastoma multiforme

Application

- 10.1. The Committee considered the application from a consumer for the funding of bevacizumab (Avastin) for the treatment of patients with relapsed or recurrent glioblastoma multiforme.

Recommendation

- 10.2. The Committee **recommended** that the application for bevacizumab as monotherapy for the treatment of patients with relapsed or recurrent glioblastoma multiforme be declined.
- 10.3. The Committee **recommended** that the funding of bevacizumab in combination with lomustine for the treatment of patients with relapsed or recurrent high-grade glioma be referred back to the Committee for consideration once data from the EORTC phase III trial has been published, and this be noted in the Committee's points for action.
- 10.4. The Decision Criteria particularly relevant to this recommendation are *(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

- 10.5. The Committee noted the application was from a consumer who themselves had glioblastoma multiforme but under different clinical circumstances not directly related to the indication, and expressed sympathy for their circumstances and thanks for the application.
- 10.6. The Committee noted that bevacizumab is a humanized monoclonal antibody that binds to and inhibits the biologic activity of vascular endothelial growth factor (VEGF)-A which may have a role in reducing tumour angiogenesis and thereby inhibiting tumour growth. However, despite the highly vascular nature of glioblastoma multiforme, a plausible biological mechanism for why bevacizumab may be useful in this condition the members considered that the mechanism by which bevacizumab crosses the blood brain barrier is unclear.
- 10.7. The Committee noted that bevacizumab is indicated for the treatment of multiple cancer types including colorectal, renal, lung, breast, ovarian, fallopian tube and cervical and as a single agent for the treatment of relapsed high-grade malignant glioma. The Committee noted that malignant or high-grade glioma refers to tumours that are classified as grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma) and grade IV (glioblastoma multiforme, GBM). The Committee noted that bevacizumab is not currently funded for any cancer indications in New Zealand.
- 10.8. The Committee noted that high grade primary brain malignancies are not curable. Current treatments (debulking surgery combined with adjuvant radiotherapy and chemotherapy) aim to reduce symptoms and prolong disease-free progression and survival times.
- 10.9. The Committee noted that in New Zealand temozolomide is currently funded for newly diagnosed GBM but not for relapsed or recurrent disease. Members noted that there appeared to be no standard international treatment protocol for relapsed or recurrent GBM.
- 10.10. The Committee noted that there were a large number of trials currently being undertaken investigating bevacizumab for the treatment of gliomas using various dose regimens. The Committee noted that the Medsafe datasheet recommended dose is 10mg/kg every 2 weeks.
- 10.11. The Committee noted the primary evidence for the use of bevacizumab in the treatment of relapsed GBM is from the AVF3708 study (published as Freidman et al. J Clin Oncol 2009;27(28):4733-40) a phase II, randomised study of bevacizumab alone or in combination with irinotecan for the treatment of GBM in first or second relapse. The Committee noted that patients were randomly assigned to receive bevacizumab (10mg/kg every 2 weeks, n=85) or in combination with irinotecan (125mg/m² or 340mg/m² if taking enzyme-inducing antiepileptic drugs, n=82) for 104 weeks or until disease progression or unacceptable toxicity. The Committee noted that eligibility criteria included histologically confirmed GBM in first or second relapse and disease progression confirmed by magnetic resonance imaging (MRI) \geq 14 days before the first study treatment, Karnofsky performance status \geq 70%; life expectancy greater than 12 weeks; adequate hematologic (ie, platelet count \geq 100,000/ μ L, absolute neutrophil count \geq 1,500/ μ L), hepatic, and renal function; and previous treatment with radiotherapy and temozolomide.
- 10.12. The Committee noted that six month PFS rates, the primary end-point of the study, were 42.6% (97.5% CI, 29.6% to 55.5%) in the monotherapy group and 50.3% (97.5% CI, 36.8% to 63.9%) in the combination group. ORR was reported as 28.2% (97.5% CI, 18.5% to 40.3%) in the monotherapy group and 37.8% (97.5% CI, 26.5% to 50.8%) in the combination group.

- 10.13. The Committee noted that median PFS was 4.2 months (95.0% CI, 2.9-5.8) for the monotherapy group and 5.6 months (95.0% CI, 4.4-6.2) for the combination group. Median OS from the time of random assignment were 9.2 months (95.0% CI, 8.2-10.7) for the monotherapy group and 8.7 months (95.0% CI, 7.8-10.9) for the combination group. The median response durations were 5.6 months (95.0% CI, 3.0-5.8 months) in the monotherapy group and 4.3 months (95.0% CI 4.2-not reached) in the combination group.
- 10.14. The Committee noted that 39 patients (46.4%) in the monotherapy group and 52 patients (65.8%) in the combination group experienced grade 3 or greater adverse events (AEs), the most common of which were hypertension (8.3%) and convulsion (6.0%) in the monotherapy group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the combination group.
- 10.15. The Committee noted that study AVF3708 provided only direct evidence comparing use of irinotecan because both randomised groups also used bevacizumab. As such the Committee considered the study provided limited evidence for the efficacy of bevacizumab. Members noted that this is a common limitation of phase II trials (designed to test whether a medicine is safe and effective) compared with the better and usable evidence in phase III trials (testing efficacy and safety compared with current treatments).
- 10.16. The Committee also considered evidence for the use of bevacizumab in the treatment of relapsed GBM from the NCI trial (Kreisl TN et al. JCO 2009;27:740-5) - a Phase II non-comparative trial of single-agent bevacizumab at a dose of 10 mg/kg every 14 days on a 28 day cycle until disease progression followed by irinotecan 340 mg/m² or 125 mg/m² every 2 weeks, depending on use of enzyme-inducing antiepileptic drugs, in 48 heavily pre-treated patients with recurrent GBM.
- 10.17. The Committee noted evidence for the use of bevacizumab in the treatment of relapsed GBM from the BELOB study (Taal and Oosterkamp et al. Lancet Oncol 2014;15:943-53) an open label, three-group, multicentre Phase II study in patients with first recurrence following treatment with temozolomide. The Committee noted that patients were randomized to receive lomustine (110mg/m² every six weeks, n=47), bevacizumab (10mg/kg every 2 weeks, n=51) or combination lomustine (110mg/m² every 6 weeks, n=8) and bevacizumab (10mg/kg every 2 weeks). The Committee noted that following a pre-planned safety analysis of patients receiving combination treatment the dose of lomustine was reduced to 90mg/m² (n=47) due to haematological AEs.
- 10.18. The Committee noted that overall survival at 9 months, the primary endpoint, was 43% (95% CI 29-57) in the lomustine monotherapy group, 38% (25-51) in the bevacizumab monotherapy group, 59% in the bevacizumab/lomustine 90mg/m² group, 87 % in the bevacizumab/lomustine 110mg/m² and 63% in all patients treated with bevacizumab plus lomustine. The Committee noted that patients received an average of 2 cycles, and that all patients receiving single-agent bevacizumab discontinued treatment during the trial period and only 3 patients receiving bevacizumab plus lomustine remained on treatment.
- 10.19. The Committee noted that the study did not include a control arm and lacked statistical power to detect important differences in outcomes between the treatment groups. The Committee considered the efficacy of bevacizumab was difficult to determine from this study. Members noted that the authors concluded the results did not support a role for single-agent bevacizumab in the treatment of recurrent GBM but that bevacizumab plus lomustine 90mg/m² combination treatment warrants further investigation in an adequately powered randomized Phase III trial.
- 10.20. The Committee noted that the evidence for the use of bevacizumab was of poor strength and quality because it came from studies which did not compare its use to a control arm and because of the relatively small numbers of patients, in comparison to the other studies of cancer. The Committee considered that the benefit of bevacizumab compared

to the current standard of care was uncertain and use of the agent was associated with a significant adverse event profile.

- 10.21. The Committee considered that bevacizumab in combination with lomustine may have greater efficacy than bevacizumab alone but the current evidence makes it difficult to determine if it would be possible to target treatment to patients who would benefit most.
- 10.22. The Committee noted that the European Organisation for Research and Treatment of Cancer (EORTC) was currently undertaking a Phase III randomised controlled trial (clinicaltrials.gov registration NCT01290939) investigating the efficacy of bevacizumab plus lomustine for relapsed GBM compared with lomustine alone. The Committee requested that PHARMAC staff arrange for published data from this trial be referred to the Committee for consideration once it became available.

11. Pomalidomide for relapsed or refractory multiple myeloma

Application

- 11.1. The Committee considered the application from Cellegene Pty Ltd for the funding of pomalidomide (Pomalyst) in combination with dexamethasone for the treatment of relapsed and refractory multiple myeloma in patients who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Recommendation

- 11.2. The Committee **recommended** that pomalidomide in combination with dexamethasone be funded with a low priority for the treatment of relapsed and refractory multiple myeloma patients who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
- 11.3. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee.
- 11.4. The Decision Criteria particularly relevant to this recommendation are *(iii) The availability and suitability of existing medicines; therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 11.5. The Committee noted that multiple myeloma (MM) is a relatively rare haematological malignancy that predominantly affects elderly patients and is currently not considered curable. The Committee noted that improved 5 year survival rates have been observed with the introduction of targeted treatments such as thalidomide, bortezomib and lenalidomide, however, all patients eventually develop resistance to these treatments and with each subsequent line of therapy response duration consistently decreases .
- 11.6. The Committee noted that pomalidomide is part of a class of immunomodulatory drugs (IMiDs) that includes thalidomide and its analogues, lenalidomide, and apremilast. The Committee noted that IMiDs inhibit tumour necrosis factor (TNF) – α and interleukin (IL)-1b, and stimulate IL-10. In addition IMiDs enhance T-cell proliferation, natural killer cell activity, T-cell activity and IL-2 production.
- 11.7. The Committee noted that pomalidomide in combination with dexamethasone is indicated for the treatment of relapsed and refractory MM in patients whose disease has progressed after at least two prior treatment regimens including lenalidomide and

bortezomib (i.e. third line treatment or higher) and have demonstrated disease progression on last therapy.

- 11.8. The Committee noted that in-vitro assays show the anti-TNF activity of pomalidomide is 50,000 times greater than that of thalidomide and 10 times greater than lenalidomide. The Committee considered there may be potential for pomalidomide to be used earlier in the treatment paradigm than the third line setting sought by the applicant but noted that it had been presented with no evidence to support its use in this way.
- 11.9. The Committee noted that the recommended initial dosage of pomalidomide is 4 mg orally once daily without food for days 1-21 of each 28 day cycle until disease progression in combination with low dose dexamethasone on days 1, 8, 15 and 22 of each cycle. The Committee noted that the dose of pomalidomide administered can be modified based on clinical and laboratory findings.
- 11.10. The Committee noted open-label dose escalation phase 1 trials established pomalidomide as being well tolerated in doses ranging from 1-5mg/day continuously (Schey et al. JCO 2004;22:3269-76) or on alternate days (Streetly et al. Br J Haematol 2008;141: 41-51) with response rates of 50% or greater.
- 11.11. The Committee noted that the recommended dose was established by the MM-002 trial - an open-label phase 1, dose escalation study to determine the maximum tolerated dose of pomalidomide given for 21 of 28 days per cycle in patients with relapsed/refractory MM (Richardson et al. Blood 2013;121:1961-7). Members noted that the patient population was heavily pre-treated with a median of 6 prior regimens, including bortezomib and lenalidomide, and that dexamethasone was added for suboptimal responses in 22 of the 38 enrolled patients.
- 11.12. The Committee noted a series of phase 2 studies which used doses of 2 mg and 4 mg continuously for 28 days with dexamethasone 40 mg with partial responses or better reported in 63% of patients treated with 2 mg daily (Lacy et al. JCO 2009;27:5008-14). Members noted that the median duration of response was 21 months and median progression-free survival (PFS) of 13 months (Lacy et al. Leukemia 2010;24:1934-9).
- 11.13. The Committee noted that the IFM2009-02 trial was a randomized phase 2 study comparing pomalidomide (4 mg for 21 of 28 days or 4 mg daily) in combination with weekly dexamethasone in 84 patients with MM refractory to both bortezomib and lenalidomide (Leleu et al. Blood 2013;121:1968-75). Members considered that overall response rate (ORR) did not appear to be dose dependent, reported as 35% and 34% respectively, with similar levels of toxicity across the two dose schedules.
- 11.14. The Committee noted the pivotal evidence for the use of pomalidomide in the treatment of relapsed/refractory MM is from the MM-003 study (primary citation: San Miguel et al. Lancet Oncol 2013;14:1055-66) a phase III multi-centre, randomized, open label study of 455 patients with relapsed and refractory MM, who had failed at least 2 previous treatments including bortezomib and lenalidomide, alone or in combination, and had progressive disease since last treatment or intolerance of bortezomib.
- 11.15. The Committee noted that exclusion criteria included: previous treatment with pomalidomide; hypersensitivity to thalidomide, lenalidomide or dexamethasone; resistance to high dose dexamethasone (HDD); or grade 2 or more peripheral neuropathy.
- 11.16. The Committee noted patients were randomized to receive either 28 day cycle pomalidomide, at a dose of 4 mg per day on days 1-21, plus low-dose dexamethasone (LDD) at a dose of 40 mg on days 1, 8, 15 and 22, (n=302) compared to high-dose dexamethasone (HDD) alone at a dose of 40 mg per day on days 1-4, 9-12, and 17-20 (n=153) until disease progression or unacceptable toxicity. The Committee noted that

patients were stratified by age, disease status and number of previous treatments. The Committee considered that HDD was not an appropriate comparator in a New Zealand setting as it is not the current standard of care in New Zealand.

- 11.17. The Committee noted that patients with progressive disease on HDD could crossover to receive pomalidomide at the same dose but without dexamethasone in the companion trial MM-003C and, at the time of final PFS analysis, patients in the HDD arm who had not progressed could crossover to receive pomalidomide with or without dexamethasone.
- 11.18. The Committee noted that, after a median follow up of 10.0 months (IQR 7.2–3.2) median PFS, the primary endpoint, was 4.0 months (95% CI 3.6-4.7) in the pomalidomide/LDD arm compared to 1.9 months (95% CI 1.9–2.2) in the HDD arm (HR 0.48, 95% CI 0.39–0.60, $p < 0.0001$). Median OS was 12.7 months (95% CI 10.4-15.5) compared to 8.1 months (95% CI 6.9-10.8) in the pomalidomide/LDD and HDD arms respectively (HR 0.74, 0.56-0.97, $p = 0.0285$). In patients with at least a partial response, median response duration was 7.0 months (95% CI 5.8-9.0) compared to 6.0 months (95% CI 1.4-8.5) in the pomalidomide/LDD and HDD arms respectively (HR 0.52, 95% 0.25-1.05, $p = 0.0631$).
- 11.19. The Committee noted that grade 3-4 haematological adverse events were reported in 48% of patients in the pomalidomide/LDD arm compared to 16% in the HDD arm and treatment-related adverse events leading to death were reported in 4% of patients in the pomalidomide/LDD arm compared to 5% of patients in the HDD arm.
- 11.20. The Committee noted that in subgroup analysis overall survival was prolonged in the pomalidomide/LDD arm versus the HDD in: women (HR 0.61; 95 % CI 0.41–0.92; $n = 121$ and 66), patients refractory to prior lenalidomide treatment (12.7 vs. 8.0 months; $p = 0.0234$; HR 0.73; 95 % CI 0.55–0.96; $n = 286$ and 141), and those with lenalidomide as their last previous therapy (HR 0.53; 95 % CI 0.33–0.87; $n = 85$ and 49)
- 11.21. The Committee noted at an updated median follow-up of 15.4 months (San Miguel et al. *Haematologica* 2015; 100:1334-9) the median OS was 13.1 months in the pomalidomide/LDD arm compared to 8.1 months (HR 0.72; $p = 0.009$) in the HDD arm. The Committee noted that this represents an increase in OS of 5 months but that the supplier states due to the degree of crossover from the HDD arm the increase in OS was 10 months.
- 11.22. The Committee noted that the results of quality of life questionnaires (general health related Eq5D HRQoL, EORTC QLQ-C30 for cancer patients, and EORTC QLQ-MY20 for myeloma patients) are reported in a separate publication. (Weisel et al. *Clin Lymphoma Myeloma Leuk.* 2015;15:519-30) and indicated that quality of life of patients with relapsed/refractory MM was likely to be poor with fatigue, bone pain and may be better with pomalidomide/LDD than HDD but was difficult to determine from the data presented.
- 11.23. The Committee noted a prospective randomized phase 2 trial evaluating clinical and pharmacodynamics effects of continuous (2 mg daily) or intermittent (4 mg for 21 days of each 28 day cycle) dosing schedules for pomalidomide and the impact of immune activation and cereblon targets in 39 patients with lenalidomide refractory MM (Sehgal et al. *Blood* 2015;125:4042-51) which reported that intermittent dosing led to greater tumor reduction at the cost of more frequent adverse events and that both cohorts experienced similar overall survival. Members considered this may indicate uncertainty regarding the optimal dose of pomalidomide.
- 11.24. The Committee noted the potential for resistance and response to lenalidomide and pomalidomide to be determined by levels of cereblon, a protein encoded by CDBN gene (Zhu et al. *Blood* 2011;118:4771-9) and considered this may represent a potential biomarker to target treatment to the patients that would benefit most but considered that at this stage the evidence to support this was weak.

- 11.25. The Committee noted there are a number of trials being undertaken investigating the use of pomalidomide in combination with other treatments including prednisone, cyclophosphamide, bortezomib, pegylated doxorubicin and carfilzomib.
- 11.26. The Committee noted that the National Comprehensive Cancer Network guidelines recommended pomalidomide plus dexamethasone may be used as salvage therapy in patients with relapsed or refractory disease and the Scottish Medicines Consortium also recommended its use, but contingent upon the continuing availability of the patient access scheme or an equivalent or lower list price. The Committee noted that the National Institute for Health and Care Excellence (UK) and the Pharmaceutical Benefits Advisory Committee (Australia) had not recommended pomalidomide be funded due to high cost and uncertain cost-effectiveness.
- 11.27. The Committee considered that evidence for the use of pomalidomide in the treatment of relapsed/refractory MM was moderate being from a single open label RCT with significant cross-over and from which it was difficult to determine an increase in OS from current standard of care. The Committee considered that treatment with pomalidomide appeared to be associated with significant risk of grade 3 or 4 adverse events that would require careful management.
- 11.28. The Committee considered that all MM patients would eventually progress past lenalidomide and considered that the majority of these patients would trial a subsequent line of treatment were one available. The Committee considered that pomalidomide might be used in combination with other treatments such as bortezomib.
- 11.29. The Committee noted that if pomalidomide were to be listed on the PS it should be restricted to haematologists only with a 4 month approval period.
- 11.30. The Committee considered the application be reviewed by the Cancer Treatments Subcommittee for further advice regarding the benefits and risks compared with currently funded treatment options in New Zealand, duration of treatment, optimal dosage and place in the treatment paradigm.

12. Velaglucerase alfa for Gaucher disease

Application

- 12.1. The Committee reviewed an application from Shire for the funding of velaglucerase alfa for the treatment of Gaucher disease.

Recommendation

- 12.2. The Committee **recommended** PHARMAC run a Request for Proposals for a first-line enzyme replacement therapy for the treatment of Gaucher disease.
- 12.3. The Committee **recommended** the Gaucher Panel be retained at this time, noting they would have an important role in any transition if a change in first-line ERT was to occur.
- 12.4. The Committee **recommended** the funding application and the PTAC minutes from this meeting be referred to the Gaucher Panel for review at their next scheduled meeting.
- 12.5. 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; (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

- 12.6. The Committee noted that Gaucher disease, a lipid storage disease is a rare disorder that presents in patients in a range of phenotypes, and severity varies widely. Members noted that Gaucher disease is typically divided into three clinical subtypes type 1 (GD1), type 2 (GD2) and type 3 (GD3). GD1 affects between 1:50,000 and 1:100,000 people, and GD 3 is estimated to be about 1:200,000. Members also noted that there are currently 20 patients receiving funded therapy for Gaucher disease in New Zealand. 18 patients have GD1, and two patients GD3.
- 12.7. The Committee noted that internationally enzyme replacement therapy (ERT) options for Gaucher disease include imiglucerase, and velaglucerase alfa. Members noted that imiglucerase (Cerezyme, supplied by Genzyme) is funded in New Zealand for eligible patients via application to the Gaucher Panel. Imiglucerase has been funded in the Pharmaceutical Schedule since 1999.
- 12.8. The Committee noted previous PTAC and Gaucher Panel meeting minutes regarding imiglucerase and the Special Authority criteria used by the Panel to assess applications for use of imiglucerase. Members noted that in New Zealand the dose of imiglucerase was lower than that used in other countries, with a maximum dose of 15 IU/kg/month for most patients, and up to 30 IU/kg/month for certain children with Gaucher disease who meet particular criteria. For any doses greater than 30 IU/kg/month, PHARMAC approval is required. Members noted standard international doses of imiglucerase for GD1 are typically between 30 and 60 IU/kg every two weeks, equivalent to between 60 and 120 IU/kg/month.
- 12.9. The Committee noted that velaglucerase alfa (VPRIV) is indicated for long-term ERT for patients with GD1. Members noted the supplier Shire, submitted an application to Medsafe in January 2015 for registration and anticipates approval in January/February 2016.
- 12.10. The Committee noted the evidence provided in the application to consist of two randomised controlled trials (RCT's), four prospective cohort studies and two retrospective cohort studies. Members noted the studies most relevant to the discussion were a RCT comparison of velaglucerase alfa and imiglucerase (Turkia H.B. et al. *Am J Hematol* 2013;88:179-84) and five cohort studies describing patients who changed from imiglucerase to velaglucerase alfa. Three of these are prospective cohort studies (Zimran et al. *Am J Hematol* 2013;88:172-8 and Elstein et al. *Am J Hematol* 2015;90:592-7, Pastores et al. *Genetics in Medicine* 2014;16:359-66, and CSR HGT-GCB-087 and HGT-GCB-091) and two are retrospective cohort studies (Elstein et al. *Blood Cells, Molecules, and Diseases* 2012;48:45-50, and van Dussen *Haematologica* 2012;97:1850-4).
- 12.11. The Committee noted the Turkia et al. (2013) RCT of 34 patients from 11 centres in nine countries. Patients had GD1, were anaemic, and with one of low platelets, enlarged spleen, or enlarged liver. No ERT was allowed within 12 months of starting the trial. Baseline characteristics were similar in the two groups. Patients received 60 IU/kg every second week of velaglucerase alfa or imiglucerase for nine months. Members noted masking was unclear apart from radiologic assessment of spleen and liver size, and missing data and protocol violations were poorly explained. The clinical relevance for choosing a non-inferiority boundary for haemoglobin (Hb) of 10 g/L was not clear. After 9 months of treatment the reported difference in Hb (97.5% lower bound CI) was 1.4 g/L (6 g/L) between the treatment arms in the intention-to-treat population. Members noted there were no reported statistically significant differences in other outcomes, although the data is difficult to interpret due to the small sample size and limited follow-up. Adverse events seemed similar with 5/17 (29%) infusion reactions in velaglucerase alfa arm and 4/17 (24%) in the imiglucerase arm. There was one reported skin reaction in the velaglucerase alfa arm. No participants developed antibodies in the velaglucerase alfa arm and four

participants (24%) developed antibodies in the imiglucerase arm, one of whom withdrew because of multiple infusion reactions.

- 12.12. The Committee noted a prospective cohort described in Zimran et al. (2013) and Elstein et al. (2015) of 40 participants from 15 centres in 5 countries. Patients had GD1 and had received at least 30 consecutive months of imiglucerase, with a stable dose for the last six months. Members noted 35% of patients were on doses < 22.5 IU/kg every second week and 18% of patients were on 60 IU/kg every second week. All patients were switched to velaglucerase alfa at the same dose as previous imiglucerase therapy and there was no washout period. After 12 months there was no important difference in Hb or other measurements in the 38 patients who continued velaglucerase alfa. One patient (2.5%) had an anaphylactoid reaction and no patients who were negative for anti-imiglucerase antibody at baseline developed anti-velaglucerase alfa antibody. Headache, nasopharyngitis, and arthralgia were reported adverse effects in between 20 and 25% of patients. The Elstein et al. (2015) follow up study described the original cohort of 38 patients followed for 10 to 50 months (median 21 months). Members noted 36/38 patients were followed for two years and most patients continued to receive the same dose that they received in the earlier study. All clinical measurements remained static. There were no dose reductions, however 10/29 (34%) of adult patients had the velaglucerase alfa dose increased at least once. These patients received between 15 and 35 IU/kg/dose before dose adjustment. Five patients (13%) experienced six infusion reactions. One patient tested positive for anti-velaglucerase alfa antibodies during the extension study, and this one person had anti-imiglucerase antibodies at baseline.
- 12.13. The Committee noted a number of cohort studies described experiences of switching ERT in Gaucher disease from imiglucerase to velaglucerase alfa in response to manufacturing problems and international stock shortages of imiglucerase in 2009/2010. The Committee noted the cohort study described in Pastores et al. 2014 was a prospective cohort study from six centres in the US. The cohort of 205 patients was nearly all switched from imiglucerase to velaglucerase alfa. Previous imiglucerase doses ranged from 15 to 60 IU/kg/ every second week, 13% received 15 IU/kg and 30% received 60 IU/kg every second week. Anti-imiglucerase antibody was present in 18% of patients and anti-velaglucerase alfa antibody in 6%. Median use of velaglucerase alfa at time of reporting was 26 weeks. Patients were switched to equivalent doses of velaglucerase alfa. There was no reported change in Hb or platelets although no data summaries were reported. Infusion-related adverse events were reported in 13% of patients following the switch. Headache, fatigue, nasopharyngitis, nausea were reported in 5 to 7% of patients. Only 1/167 (0.6%) patient developed anti-velaglucerase alfa antibody and this patient was anti-imiglucerase antibody positive at baseline.
- 12.14. The Committee noted a prospective cohort study reported in CSR HGT-GCB-087 and HGT-GCB-091 were of six patients (two adults and four children) recruited from three centres in Japan who were all swapped from imiglucerase to velaglucerase alfa at the same dose. Hb and platelets were stable at one and two years, and no anti-velaglucerase alfa antibodies were reported. One patient may have had an infusion reaction.
- 12.15. The Committee noted a retrospective cohort study (Elstein et al. 2012) of 71 patients from a single centre in Israel who were swapped from imiglucerase or newly started on velaglucerase alfa. Members noted detailed data was only given for 44 patients and this was split by 'switched' or 'naïve'. From the data available Hb appeared to be unchanged in the patients who had switched treatment and spleen and liver volume measurements had reduced. One patient had a drug-related adverse reaction after the first dose received.
- 12.16. Members noted another retrospective cohort study of 32 patients (van Dussen et al. 2012) from two centres (UK and Netherlands) switched from imiglucerase to velaglucerase alfa. Patients received velaglucerase alfa doses equivalent to imiglucerase doses before the

imiglucerase shortage. Prior to the study, all patients had received reduced imiglucerase doses due to the shortage (range 1 to 8 months), and 13 patients had stopped treatment for a short period of time before they started velaglucerase alfa. Results were therefore more difficult to interpret, though Hb and platelet count generally remained stable.

- 12.17. The Committee noted several other studies, an RCT of two dosing regimens of velaglucerase alfa (Gonzalez et al. *Am J Hematol.* 2012;88:166-71) and a cohort study in patients who had not been on imiglucerase for 12 months (Zimran et al. *Blood* 2010;115:4651-6 and Zimran et al. *Am J Hematol.* 2015;90:577-83)
- Gonzalez et al. 2013 was a RCT of 25 patients from 5 centres in 5 countries comparing two doses of velaglucerase alfa, 60 IU/kg per fortnight and 45 IU/kg every second week for a year. Members noted one patient in each treatment arm was later identified as a Gaucher carrier only. The mean (SD) change in baseline Hb for all patients was 24 (11) and 24.2 (15.8) g/L; difference -0.2 (95% CI -11.4 to 11.1). Members noted there was minimal difference if the non-Gaucher patients were excluded. There were 14 infusion events in 25 participants and 1 patient (4%) developed anti-velaglucerase alfa antibodies.
 - A prospective cohort described in Zimran et al. 2013 and Zimran et al. 2015 was originally of 12 participants with Gaucher disease from a single centre in Israel. Patients were either treatment naïve or free of imiglucerase use for 12 months and anti-imiglucerase antibody negative. The dosing of velaglucerase alfa was complex starting at 15 IU/kg every second week, increasing to 60 IU/kg/ dose and then back-titration from 6 to 9 months. The mean (SD) change in Hb from baseline after 9 months was 23.3 (8.9). In eleven patients, similar changes were seen at 24 and 48 months and at about 6 to 7 years. No anti-velaglucerase alfa antibodies were reported and most patients seemed to have a dose reduction to 30 IU/kg every second week by about 20 months.
- 12.18. The Committee noted overall the evidence was of good strength and moderate quality to indicate that that velaglucerase alfa has the same therapeutic effect as imiglucerase. The Committee considered that based on the evidence reviewed, if patients switched from imiglucerase to velaglucerase alfa, it would have a similar or same effect at the same dose. Members noted New Zealand uses lower dosing of imiglucerase compared to other countries and considered equivalent dosing would be possible with velaglucerase alfa. Members considered determining a maximum dose would be a fiscal decision, and if significant price reductions were achieved then it could result in wider access to allow for higher IU/kg dosing of velaglucerase alfa, particularly in those that would benefit most, such as younger patients.
- 12.19. The Committee considered overall there would be no additional clinical benefit from velaglucerase alfa compared to current treatment with imiglucerase. There may potentially be less antibody formation and infusion reactions with velaglucerase alfa, however the evidence to support this is poor.
- 12.20. The Committee noted that the total annual cost and average cost per patient of imiglucerase has steadily increased over the last 9 years. Members noted any infusion time efficiency gains for DHBs with velaglucerase alfa would be unlikely as imiglucerase is often given over 60 minutes, particularly given the lower doses used in New Zealand and this is a similar period to velaglucerase alfa. Members noted non-pharmaceutical costs would be expected to be similar for either drug.
- 12.21. Members noted funded access to imiglucerase was widened in September 2013 to include patients with GD3 who exhibit clinically significant non-neurological manifestations of the disease. Velaglucerase alfa is not approved for the treatment of GD3 internationally, however members considered it would be reasonable to consider switching GD3 patients currently on imiglucerase to velaglucerase alfa if a change in first-line ERT for Gaucher disease was to occur.

- 12.22. The Committee considered whether development of antibodies would affect patient outcomes and considered that there was weak evidence to support that the development of antibodies to ERT would require patients to switch to an alternative ERT.
- 12.23. Members considered there were some uncertainties regarding how best to manage switching patients from imiglucerase to velaglucerase alfa if a change was to occur. Members noted there may be increased monitoring requirements, extra clinic time and some patients that potentially could not to switch. Members noted the Gaucher Panel would be well placed to consider these issues.
- 12.24. The Committee noted there were no issues with access to currently funded imiglucerase via the Gaucher Panel. The Committee noted there was significant uncertainty around dosing of imiglucerase and the Panel acted an independent system to manage dosing and provide clinical oversight and consistency. Members noted the Gaucher Panel had a unique position in managing the significant fiscal risk of imiglucerase. The Committee recommended the Gaucher Panel be retained at this time, noting they would have an important role in any transition if a change in first-line ERT was to occur. The Committee considered a shift to a standard Special Authority restriction could be possible in the future if there was less fiscal uncertainty for Gaucher treatments.

13. Micronised progesterone for menopause hormone therapy (MHT)

Application

- 13.1. The Committee reviewed a funding application from Pharmaco (NZ) for micronised progesterone (Utrogestan) for use in Menopause Hormone Therapy (MHT).

Recommendation

- 13.2. The Committee **recommended** that the application for the funding of micronised progesterone (Utrogestan) on the Pharmaceutical Schedule for use in Menopause Hormone Therapy (MHT) be declined.
- 13.3. 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

- 13.4. The Committee noted that the supplier had resubmitted an application for micronised progesterone (Utrogestan) for use in Menopause Hormone Therapy (MHT) on the basis that there was further supportive evidence to show improved cardiovascular risk. The Committee noted the previous application had been submitted in July 2012 for the same indication and had been declined at that meeting by Committee members.
- 13.5. The Committee noted that progestogens are synthetic forms of progesterone and that Utrogestan is a micronised progesterone. The Committee considered micronised progesterone has a reduced particle size compared to other progestogens and that micro-ionisation may increase bioavailability of the product.
- 13.6. The Committee noted the suppliers estimate of numbers of New Zealand women on MHT was between 14,600 (5%) to 29,300 (10%) of women in the menopausal age range. The Committee further noted that in 2015 PHARMAC numbers indicated that 45,138 patients were dispensed MHT. The Committee considered that the supplier likely underestimated the number of patients who use MHT in New Zealand.

- 13.7. The Committee noted that oestrogen is the most effective agent in MHT, however for women with an intact uterus progestogens are prescribed with oestrogen.
- 13.8. The Committee noted that there were funded progestogens available for prescribing in MHT on the Pharmaceutical Schedule, including medroxyprogesterone acetate (MPA) and norethisterone. The Committee considered there was a significant price difference between the currently funded progestogens and the suppliers proposed subsidy of \$16.50 for 30 capsules of Utrogestan.
- 13.9. The Committee considered that the new evidence provided by the supplier in support of this application to be of weak strength and low quality and was limited to a small number of studies of progesterones in general rather than oral micronised progesterone in particular.
- 13.10. The Committee noted a Quality Of Life (QOL) cross-sectional survey of 176 women, comparing MHT regimens containing oral micronised progesterone with medroxyprogesterone acetate (Fitzpatrick L, J Womens Health Gen Based Med. 2000;9: 381-7). Members noted that this was a cross-sectional survey examining QOL related to physiological, somatic and vasomotor effects of changing progestogen treatment from MPA to micronised progesterone in post-menopausal women. The Committee noted that women reported improved perceptions of menopausal symptoms whilst on micronised progesterone. The Committee considered that this provided low quality supportive data for the use of micronised progesterone in MHT. The Committee further considered the application would have been better if the supplier could have identified and provided evidence of a robust QOL benefit for micronised progesterone such as from a well-performed cohort study or a randomised controlled trial.
- 13.11. The Committee noted a review re-evaluating the findings from the 2002 Women's Health Initiative, which had shown an increase in the rate of breast cancer and cardiovascular risks, with use of HRT (Rossouw et al, Obstet Gynecol. 2013;121:172-6). Members considered that the re-evaluation showed that MHT assisted the relief of vasomotor symptoms but was not recommended for prevention of coronary heart disease.
- 13.12. The Committee noted a randomised controlled trial, which was a sub-analysis of the Kronos Early Estrogen Prevention Study (KEEPS), assessing the atherosclerosis progression and cardiovascular disease risk factors in 727 healthy recently menopausal women (Harman et al, Ann Intern Med, 2014; 161:249-60). Members noted the primary endpoint for the study was annual change in carotid artery intima-media thickness (CIMT) and the secondary endpoint included changes in markers of cardiovascular disease. Members noted that women were randomised to receive either oral conjugated equine oestrogens 0.45 mg daily or transdermal oestradiol, 50 mcg daily, each with 200 mg of oral progesterone for 12 days per month or placebo for 48 months. Members noted that overall 79.8% of the 727 patients had a CIMT at 48 months and mean CIMT increases were similar across groups. Members further noted the proportions of patients in whom coronary artery calcium (CAC) increased did not differ significantly across the groups and the serious adverse events did not differ between the different therapy regimens. Members considered that the trial indicated MHT reduced vasomotor events but noted that full data of the trial was not presented.
- 13.13. The Committee noted an abstract to the Early Versus Late Intervention Trial with Estradiol (ELITE) study, a randomised double blind placebo controlled trial determining the effect of MHT on slowing the progression of subclinical atherosclerosis (Hodis et al, Epidemiology and Prevention of Cardiovascular Disease: Physiology, Pharmacology and Lifestyle, 2014; 130: Abstract 13283). Members noted there were 643 healthy postmenopausal women in the study randomised to either 1 mg oral oestradiol with 10 days of 45 mg vaginal micronised progesterone gel for those women with an intact uterus. The primary endpoint was progression of carotid artery intima media thickness (CIMT) measured from baseline and then 6 monthly up to 6 years. Members noted that women who commenced

MHT at the debut of or early in menopause (median 3.5 years) showed a significant reduction relative to placebo of CIMT compared to no effect when initiated late after the menopause. Members considered that this was a surrogate endpoint and it was difficult to derive what the small difference in CIMT actually meant. Members noted the full study is awaiting publication.

- 13.14. The Committee noted a cohort study that assessed whether different oral progestogens in hormone replacement therapy may differentially affect the risk of endometrial cancer (Fournier et al, Am J Epidemiol, 2014; 180:508-17). Members noted that study data was taken from 65,630 post-menopausal women between 1992-2008 in whom 301 endometrial cancers occurred. Members further noted that hazard ratios and their confidence intervals were derived from Cox models. Members noted that compared with never use of hormone replacement therapy, ever use of oestrogen and micronised progesterone was associated with an increased risk of endometrial cancer (hazard ratio (HR) =1.80, 95% confidence interval (CI): 1.38, 2.34) that was significantly more marked with longer duration of use. Users of preparations containing other progesterone derivatives or a nonsteroid derivative were not at significantly increased risk (HR = 0.79 (95% CI: 0.60, 1.05) and HR = 1.30 (95% CI: 0.85, 1.99) respectively). Members considered that this study indicates micronised progesterone does not decrease the risk of endometrial cancer.
- 13.15. The Committee noted a population-based case-control study of the breast cancer risk by MHT regimen in post-menopausal women (Cordina-Duverger et al, PLoS One 2013; 8: e78016). Members noted the study included 1555 women of whom there were 739 cases and 816 controls. The case group included incident cases of insitu or invasive breast cancer diagnosed between April 2005 and March 2007 in women aged 25-75 years (only menopausal women were included in the analysis). Members noted the study showed that for users of Estrogen-Progestogen (EP) therapy containing a natural micronised progesterone the odds ratio was < 1 and synthetic progestagen showed an odds ratio of 1.57 (confidence interval 0.99-2.49) for progesterone derived and 3.35 (1.07 – 10.4) for testosterone-derived progestogen. Members considered that testosterone-derived progestogens may increase the risk of breast cancer however these progestogens are taken continuously, which was previously associated with an increased risk of breast cancer. Members noted that EP therapies that are prescribed containing natural progesterone were not associated with an increased risk of breast cancer.
- 13.16. The Committee considered that overall there was insufficient evidence regarding both patient safety profile or therapeutic efficacy of oral micronised progesterone to support funding at this time. Members considered that there may be a patient preference for the use of micronised progesterone but due to poor QOL data presented with the application this was difficult to determine. Members further considered that the subsidy of Utrogestan would be a significant net cost to the Pharmaceutical Schedule over and above the currently funded progestogens. The Committee did not support funding for this oral micronised progesterone.

14. Methoxyflurane (Penthrox) for community listing on Practitioner's Supply Order (PSO) and safety update

Application

- 14.1. The Committee considered an application from Douglas Pharmaceuticals to widen funded access for methoxyflurane (Penthrox) to the community setting on a Practitioners Supply Order (PSO). The Committee also considered a review of safety information gathered by PHARMAC staff for methoxyflurane following the listing on the HML from 1 July 2013.

Recommendation

- 14.2. The Committee **recommended** that methoxyflurane (Penthrox) be listed in Section E, Part I of the Pharmaceutical Schedule, allowing funded access in the community on a Practitioners Supply Order (PSO), with a low priority.
- 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 14.4. The Committee noted that methoxyflurane (Penthrox) is supplied as a 3 mL sealed bottle containing methoxyflurane solution and a hand-held plastic inhaler. Methoxyflurane is indicated for emergency relief of pain in conscious haemodynamically stable patients, under supervision of personnel trained in its use, and for the relief of pain in monitored conscious patients who require analgesia for minor surgical procedures such as dressing changes.
- 14.5. The Committee noted that the maximum recommended dose of up to 6 mL (2 x 3 mL bottles) of methoxyflurane per 24 hours, and 15 mL (5 x 3 mL bottles) per week should not be exceeded to avoid renal toxicity.
- 14.6. The Committee noted that methoxyflurane was listed on the HML from 1 July 2013, subject to restrictions limiting its use to patients undergoing painful procedures with an expected duration of less than one hour, under the supervision of a medical practitioner or nurse who is trained in the use of methoxyflurane.
- 14.7. The Committee noted that methoxyflurane is currently being used in New Zealand in the acute pain setting for analgesia in ambulance services, the military, and emergency departments, along with use in some DHB hospitals as an analgesic for procedural sedation.
- 14.8. The Committee noted the results of a randomised, double-blind, multicentre, placebo-controlled trial by Coffey et al. (Emerg Med J. 2014;31:613-8) involving 300 patients, 90 of whom were adolescents (aged 12–17 years), who presented to six emergency department sites in the UK with pain associated with minor to moderate trauma. Participants were well matched for baseline demographics. The Committee noted that methoxyflurane reduced pain severity (measured on a visual analogue scale (VAS)) significantly more than placebo at all time points tested, with the greatest estimated treatment effect observed 15 min after the start of treatment. Overall adjusted change from baseline was -30.2/100 in the methoxyflurane group versus -15.2/100 in the placebo group, with an overall treatment effect of -15.1/100 (95% CI, -19.2 to -11 minutes; $p < 0.0001$). The time to first pain relief was four minutes for methoxyflurane (95% CI, 2 to 5 minutes) and ten minutes for placebo (95% CI, 5 to 12 minutes). The Committee further noted that rescue medication was required less in the methoxyflurane group and that patients, physicians and nurses rated methoxyflurane better than placebo. The Committee considered the change in pain scores with methoxyflurane to be clinically relevant.
- 14.9. The Committee noted the results of a prospective randomized, non-blinded crossover design trial by Abdullah and colleagues (Aust Dent J. 2011;56:296-301) comparing sedation with methoxyflurane versus Entonox (50% nitrous oxide, 50% oxygen) in 20 patients undergoing premolar extraction. The Committee noted that the levels of sedation were comparable with Entonox and methoxyflurane, however the study did not look at analgesic efficacy and was therefore of little relevance. No patient using either treatment

was deeply sedated or had an oxygen saturation of less than 92%. The Committee noted that patients reported a general preference for methoxyflurane inhalation.

- 14.10. The Committee noted the results of a non-experimental case series by Buntine et al. (Emerg Med Australas. 2007;19:509-14) looking at pre-hospital use of methoxyflurane in ambulances over a ten month period. A total of 83 adults were included with the most common indications for use being acute musculoskeletal injury (41.0%), visceral pain (31.3%) and back pain (16.9%). Administration duration was 10 to 75 minutes. The Committee noted variable concentrations were given as the dilutor hole remained open in 49 patients (concentration 0.2-0.4%) and closed in 34 patients (concentration 0.5-0.7%) and 18 patients were co-administered oxygen which can increase the evaporation of agent into ambient air. The Committee expressed concern that one patient was observed to have a RSS of 5 following methoxyflurane administration and may have required airway support. The Committee noted that a high proportion of paramedics and patients were satisfied with methoxyflurane treatment.
- 14.11. The Committee noted the results of an retrospective case series by Johnston et al. (Emerg Med J. 2011;28:57-63) who analysed the analgesic effect and changes in vital signs associated with administration of inhaled methoxyflurane and/or intranasal fentanyl in 1024 prehospital patients with visceral pain. Systolic blood pressure, pulse rate, respiration rate and Glasgow Coma Scale score were assessed and remained stable in the majority of patients. Three patients administered intranasal fentanyl and one administered intranasal fentanyl and methoxyflurane were considered hypotensive five minutes after analgesic administration. On hospital arrival, ten patients administered intranasal fentanyl had entered the hypotensive range, with three of these patients also given methoxyflurane. The Committee considered that this study provided evidence that methoxyflurane has a faster onset but shorter duration of action compared to intranasal fentanyl, and that using both treatments in combination did not provide any additional benefit over monotherapy.
- 14.12. The Committee noted the results of a non-experimental case series by Babl et al. (Emerg Med Australas. 2006;18:404-10) who analysed prehospital methoxyflurane use in 105 children aged 15 months to 17 years (median age 11 years). Methoxyflurane was mainly used for extremity injuries (82%) for a median duration of 20 minutes (3-81 minutes). The Committee considered the average reduction in pain score from 7.9 (95% CI 7.5-8.3) to 4.5 (95% CI 3.9-5) at two to five minutes and to 3.2 (95% CI 2.8-3.7) at ten minutes was clinically significant, but expressed concern that only 46.6% of children under five years of age used the device appropriately. Members questioned the validity of patient-reported pain scores in sedated patients in this study. The Committee noted that 9.5% of children also received intravenous morphine in addition to methoxyflurane. The Committee also noted that patients, parents and paramedics reported high levels of satisfaction with methoxyflurane.
- 14.13. The committee noted that although no serious adverse events were recorded in the Babl et al. case series, 5/15 children aged less than 5 years and 7/88 in children aged greater than 5 years were deeply sedated. The Committee considered for this reason methoxyflurane should always be used under direct supervision by health professionals trained in airway management and additional caution would be required if using methoxyflurane in young children.
- 14.14. The Committee noted that 2.5-3 million patients in Australia and New Zealand have used methoxyflurane since its introduction in 1978. The Committee also reviewed safety information including a review by Dayan (Hum Exp Toxicol. 2016;35:91-100), a large cohort study in the prehospital setting by Jacobs (TOEMJ. 2010;3:7-13), two safety reports produced by the manufacturer, information collected from some DHBs by PHARMAC staff, and two adverse event reports from the Centre for Adverse Reactions Monitoring (CARM). Based on this information, the Committee concluded that when methoxyflurane is given in sub-anaesthetic doses by inhaler it appears to be generally

safe, and does not carry a risk of nephrotoxicity or significant occupational exposure for healthcare workers, however the Committee considered that methoxyflurane should be viewed as a low-dose anaesthetic which does carry an inherent dose-related risk of deep sedation.

- 14.15. The Committee noted that the potential advantages of methoxyflurane include a rapid onset and offset of action, comparable potency to opioid analgesics, ease of administration, patient self-regulation, no respiratory depression or clinically significant changes in vital signs, portability, and a reduced risk of needle-stick or glass vial injury to health professionals. The Committee also noted the high levels of satisfaction amongst a small number of New Zealand General Practitioners who participated in a supplier initiated product familiarisation program.
- 14.16. The Committee noted that the potential alternative analgesic agents in the community include opioid analgesics, Entonox, topical local anaesthetics, and mild non-opioid analgesics such as paracetamol and NSAIDs. The Committee noted that funded access to fentanyl injections on PSO is restricted to general practitioners working in rural areas. Furthermore, the mucosal atomizer device's that can be attached to a syringe to enable intranasal administration of fentanyl are not funded. The Committee also noted that although nitrous oxide has similar efficacy to methoxyflurane it requires bulky equipment and is not available in many primary care settings. The Committee considered that the onset of action of parenteral morphine and pethidine is relatively slow compared to methoxyflurane. Non-opioid analgesics do not have sufficient efficacy to treat the majority of acute painful situations where methoxyflurane use would be considered.
- 14.17. The Committee considered the most appropriate comparator in the community setting to be intranasal fentanyl, which likely has similar efficacy, but a longer duration of action. Members noted that intranasal fentanyl has been shown to be effective in multiple studies including a 2014 Cochrane review in children with acute pain (Murphy et al. Cochrane Database Syst Rev. 2014;10:CD009942). The Committee noted that intranasal fentanyl may cause nasal irritation/discomfort. .
- 14.18. The Committee considered that overall there is moderate quality evidence for methoxyflurane reducing pain scores in hospital, but the evidence for use in the pre-hospital setting is generally of a lower quality. The Committee considered that there is a potential risk of inappropriate use or abuse with increasing availability of methoxyflurane as identified by Grindlay & Babl (Emerg Med Australas. 2009;21:4-11), and this would need to be carefully managed.
- 14.19. The Committee considered that the range of situations and procedures where methoxyflurane could potentially be used in the community if unrestricted could be considerable and was difficult to predict.
- 14.20. The Committee noted that funded treatments for acute pain in non-rural community general practice settings are limited. The Committee considered that while it would be advantageous to have the same access to acute pain treatments in the community setting as in hospitals, the uptake of methoxyflurane, which is considerably more expensive per unit than alternatives, would be potentially high if listed on the PSO.
- 14.21. The Committee considered that the patient group who would benefit most from availability of methoxyflurane in the community would be those patients in rural general practice settings undergoing painful procedures or receiving emergency treatment for painful traumatic injuries prior to hospital transfer.

15. Removal of Special Authority criteria for ticagrelor

Application

- 15.1. The Committee considered an application from AstraZeneca Limited to remove the Special Authority restrictions from ticagrelor (Brilinta) in Pharmaceutical Schedule.

Recommendation

- 15.2. The Committee **recommended** that application to remove the Special Authority restrictions from ticagrelor (Brilinta) be declined.
- 15.3. The Committee recommended that extended ticagrelor treatment beyond 12 months following an acute coronary syndrome (ACS) event (with either 60 mg or 90 mg twice daily) be referred to the Cardiovascular Subcommittee for further consideration.
- 15.4. 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 15.5. The Committee noted that ticagrelor is currently listed in the Pharmaceutical Schedule with a Special Authority restriction limiting treatment with ticagrelor to 12 months duration following an ACS event. For initiation, the patient needs to have recently been diagnosed with an ST-elevation or a non-ST-elevation acute coronary syndrome. Renewals are possible if a new event occurs. The Committee considered that ticagrelor is almost always used in combination with aspirin, with the most-likely alternative treatment being clopidogrel plus aspirin.
- 15.6. The Committee noted that overall ACS incidence in New Zealand is falling despite the ageing of the population in general, but that the incidence is not falling for Māori and Pacific peoples. There are approximately 16,000 hospital admissions per year for ACS which is comprised of approximately 8,000 patients admitted for non ST-segment elevation myocardial infarction (NSTEMI), 6,000 for unstable angina and 2,000 for ST-segment elevation myocardial infarction (STEMI). The Committee noted that ticagrelor is not currently funded for unstable angina, and a significant increase in ticagrelor usage for this indication may result if the Special Authority was removed.
- 15.7. The Committee noted it had previously considered the results and limitations of the PLATO trial (Wallentin L et al. N Engl J Med 2009;361:1045-57) which provides the majority of the evidence for ticagrelor following ACS up to a duration of 12 months. The Committee noted the PLATO trial was a multicentre, double-blind, double dummy randomised trial involving 18,624 patients admitted to hospital with an acute coronary syndrome, with or without ST-segment elevation. PLATO study participants were randomised to receive ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily plus a placebo tablet once daily, in addition to other therapies including aspirin.
- 15.8. The Committee noted a recent paper by Brophy J (Int J Cardiol. 2015;187:600-3) describing the potential limitations of large multicentre trials such as PLATO. The Committee reiterated its previous advice that it is reasonable to suggest that ticagrelor provides a clinical benefit over clopidogrel, but the benefit in New Zealand is likely to be smaller than observed in the PLATO trial.
- 15.9. The Committee noted the results of the PEGASUS-TIMI trial by Bonaca et al. (N Engl J Med. 2015 ;372:1791-800) in which 21,162 people patients who had had a myocardial infarction one to three years previously were randomised to receive ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. Median follow up

was 33 months. The Committee noted that the addition of 90 mg ticagrelor twice daily significantly reduced the risk of cardiovascular death, myocardial infarction and stroke with Kaplan–Meier rate at 3 years of 7.85%, versus a rate in the placebo group of 9.04% (HR 0.85; 95% confidence interval [CI], 0.75 to 0.96; P = 0.008). Ticagrelor 90 mg twice daily increased the risk of major bleeding versus placebo (2.60% and 1.06% respectively; P < 0.001). The incidence of fatal bleeding or non-fatal intracranial bleeding was not significantly increased in the treatment groups.

- 15.10. The Committee noted the PEGASUS-TIMI trial also provides some evidence of a similar benefit for the 60 mg strength of ticagrelor taken twice daily, with a slightly lower bleeding risk than 90 mg. The Committee noted that a New Medicine Application for the ticagrelor 60 mg formulation was submitted to Medsafe for registration in New Zealand in August 2015. The Committee considered that if the 90 mg tablet was available unrestricted, it is likely it would be used for a periods longer than 12 months, despite not having a registered indication for this duration.
- 15.11. The Committee noted that Mauri et al. (N Engl J Med. 2014;371:2155-66) examined the outcomes of 9961 patients who after 12 months either continued dual antiplatelet therapy (DAPT) with clopidogrel or prasugrel or moved to aspirin alone. Participants had all undergone coronary stenting with drug-eluting stent and one year of treatment with DAPT before randomisation. Continued treatment with DAPT, as compared with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio, 0.29 [95% confidence interval {CI}, 0.17 to 0.48]; P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; P<0.001). The rate of moderate or severe bleeding was increased with continued DAPT treatment (2.5% vs. 1.6%, P = 0.001). The Committee considered that although this trial provided some evidence of extended DAPT efficacy, as it did not include ticagrelor, it is of limited applicability.
- 15.12. The Committee noted the results of the ARCTIC-Interruption study by Collet and colleagues (Lancet. 2014;384:1577-85) who performed an extension of the previously published ARCTIC-Monitoring trial in which 12 months of DAPT with clopidogrel or prasugrel was compared to aspirin alone following percutaneous coronary intervention (PCI) with a drug-eluting stent. In the ARCTIC-Interruption study 1259 eligible patients were randomly allocated to the interruption or continuation groups. After a median follow-up of 17 months, the primary endpoint occurred in 27 (4%) patients in the interruption group and 24 (4%) patients in the continuation group (hazard ratio [HR] 1.17 [95% CI 0.68–2.03]; p=0.58). Major bleeding events occurred more often in the continuation group.
- 15.13. The Committee noted a meta-analysis by Navarese and colleagues (BMJ. 2015;350:h1618) which included 10 randomised controlled trials (n=32,287) examining the benefits and risks of short term (<12 months) or extended (>12 months) DAPT versus standard 12 month therapy following percutaneous coronary intervention with drug eluting stents. The Committee noted most of the included studies were for clopidogrel rather than ticagrelor, limiting the applicability. The authors concluded that compared with a standard 12 month duration, short term DAPT (<12 months) after drug eluting stent implementation yields reduced bleeding with no apparent increase in ischaemic complications, and could be considered for most patients. In selected patients with low bleeding risk and very high ischaemic risk, extended DAPT (>12 months) could be considered.
- 15.14. The Committee considered that although the Special Authority process does increase the administration required, it is unlikely that any eligible patients for whom a clinical decision is made to commence ticagrelor would not receive ticagrelor as a result of the Special Authority process.
- 15.15. The Committee considered that the overall strength of evidence for extended ticagrelor treatment beyond 12 months following ACS remains weak. The Committee noted that the

almost all patients, unless presenting with a subsequent ACS event, have been discharged from specialist cardiologist care within three to six months. The Committee considered that if the Special Authority was removed there is a considerable risk that many patients would remain on ticagrelor treatment, possibly inadvertently, which carries a significantly elevated risk of bleeding. Members considered that removing the Special Authority would likely result in significant growth in the ticagrelor market.

- 15.16. The Committee considered that based on the available evidence, prolonged DAPT beyond 12 months, which ticagrelor is one option, may provide some additional health benefit for selected patients with a very high ischaemic but low bleeding risk. The Committee considered that the potential improvement in outcomes this group obtained with extended ticagrelor treatment, based on the currently limited evidence, would not in itself justify the removal of the Special Authority criteria considering the other clinical and fiscal risks associated with dosing so.

16. Varenicline (Champix) for smoking cessation

Application

- 16.1. The Committee considered an application from Pfizer New Zealand Limited to widen access to varenicline tartrate (Champix) for the treatment of smoking cessation, and to list a new pack size.

Recommendation

- 16.2. The Committee **recommended** that the application to widen funded access to varenicline (Champix) for smoking cessation to allow an additional 12 weeks of follow-on (maintenance) treatment for people who are abstinent from smoking following an initial 12 weeks' treatment be declined.
- 16.3. 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 Schedule.*
- 16.4. The Committee **recommended** that funded access to varenicline (Champix) for smoking cessation be widened to reduce the re-treatment interval from 12 to 6 months (which would permit a funded 12-week course every six months rather than every 12 months) with a low priority.
- 16.5. 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; (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 Schedule.*
- 16.6. The Committee **recommended** that the current two-week 'starter' and 'follow-on' packs of varenicline be replaced with a four-week 'initiation' pack only if this was cost-neutral or cost-saving to the Combined Pharmaceuticals Budget.
- 16.7. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of*

existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule.

Discussion

- 16.8. The Committee noted that tobacco smoking is a major cause of preventable morbidity and mortality in New Zealand. The Committee noted that smoking is driver of significant ethnic and socioeconomic health disparities, and contributes to negative outcomes for pregnant women and their babies and for children and others exposed to cigarette smoke.
- 16.9. The Committee noted that, according to the 2014/15 New Zealand Health Survey, 16.6% of adults are current cigarette smokers. Smoking prevalence was significantly higher among Māori and Pacific peoples (38.1% and 24.7%, respectively). Among Māori, smoking prevalence is higher for women (41.8%) than for men (34.0%). Because of this, tobacco use has a particularly adverse impact on the health of Māori and Pacific peoples and especially on Māori women.
- 16.10. The Committee noted that “Better help for smokers to quit” is a Government Health Target and that smoking cessation therapies have an important part to play in achieving the Government's goal of New Zealand becoming smokefree by 2025. The Committee considered that important changes still need to happen at a Governmental and societal level to realise this goal. Options include plain packaging of cigarettes, reducing the nicotine content of cigarettes, increased taxes on cigarettes, reducing the number of retail outlets selling tobacco, assessment of other modalities such as e-cigarettes and changing societal norms. The Committee considered that reaching Pacific people, Māori and especially young Māori women is a particular challenge.
- 16.11. The Committee noted that varenicline has been funded since November 2010. It is funded as a second or third-line treatment for smoking cessation, subject to Special Authority criteria. Funding is limited to a single 12-week course within a 12-month period.
- 16.12. The Committee noted that the cost of a smoking cessation attempt with varenicline is considerably higher than the other most commonly used funded treatment, nicotine replacement therapy (NRT; nicotine patches, gum and lozenges). The Committee noted that expenditure on varenicline was substantially higher than originally estimated, such that it was currently one of the top 20 expenditure items on the Pharmaceutical Schedule.
- 16.13. The Committee noted that the Special Authority criteria for varenicline require that the patient enrolls in a comprehensive support and counselling smoking cessation programme, which includes prescriber or nurse monitoring. The Committee considered that this was appropriate, as this was in line with the support that patients received in the clinical trials of varenicline on which the funding decision was based. However, the Committee considered that patients with varenicline Special Authority approvals may not receive any counselling and noted that there is no mechanism in place to verify whether patients prescribed 12 weeks of treatment contact a cessation support service. The Committee considered that smoking cessation consultations in primary care are frequently brief interventions of a few minutes' duration, often with the subject of the consultation is not smoking cessation but other complex health concerns. The Committee considered that the result of this is that the one-year quit rates with varenicline in the 'real world' setting in New Zealand are likely to be substantially lower than seen in the clinical trials (where counselling was provided weekly and the clinical context was not that of a time-poor General Practice consultation).

- 16.14. The Committee noted that the supplier, Pfizer New Zealand Ltd, had requested three changes to the funding of varenicline for smoking cessation, discussed separately below.
- 16.15. Request to widen access to varenicline to allow an additional 12 weeks of follow-on (maintenance) treatment for people who are abstinent from smoking following an initial 12 weeks' treatment
- 16.16. The Committee noted that the key evidence provided by the supplier in support of this request is study A3051035 (Tonstad et al, JAMA 2006;296:64-71). This was a double-blind, placebo-controlled, multi-centre randomised controlled trial involving 1927 cigarette smokers who were treated for 12 weeks with open-label varenicline titrated to 1 mg twice daily. Of these, 64.1% (1236 participants) were abstinent for at least the last 7 days of the 12 week period, and 1210 of these participants were then randomised to varenicline 1 mg twice daily or placebo for an additional 12 weeks. The primary efficacy endpoint was carbon monoxide (CO)-confirmed continuous abstinence for weeks 13-24 and a secondary endpoint was continuous abstinence for weeks 13-52 of the trial.
- 16.17. Participants were aged 18-75 years (mean 45 years), smoked >10 cigarettes/day during the past year, with no periods of abstinence greater than three months in the past year and who were motivated to stop smoking. More than 95% of participants were Caucasian. Participants were healthy. Exclusions were participants with a serious or unstable disease in the last six months, depression requiring treatment in the last 12 months, a history of panic disorder/psychosis/bipolar affective disorder, severe chronic obstructive pulmonary disease, history of cancer, cardiovascular disease within past six months, uncontrolled hypertension, history of drug/alcohol dependence within the last 12 months or body mass index > 38. The Committee noted that these exclusion criteria are common to varenicline trials, limiting the transferability to real world contexts.
- 16.18. Participants attended clinic visits weekly from weeks 1-8 and at weeks 10 and 12. At each clinic visit participants received up to 10 minutes of smoking cessation counselling. A further 5 clinic visits were scheduled between week 13 and 24. Participants were then followed for a further 28 weeks of non-treatment observation with a further 5 clinic visits and 4 telephone calls. The Committee noted that this level of intensive counselling is a feature of most smoking cessation pharmacotherapy trials and this too limits the transferability of this trial data to real world situations.
- 16.19. The continuous abstinence rate was statistically significantly higher for the varenicline group for weeks 13-24 (70.5% vs 49.6%; OR 2.48; 95% CI 1.95-3.16; p<0.001) and for weeks 13-52 (43.6% vs 36.9% [an absolute difference of 6.7%]); OR 1.34; 95% CI 1.06-1.69, p=0.02). Nausea was the most common reason to discontinue varenicline and 11.9% of participants discontinued during the open-label phase due to side-effects. Varenicline was generally well tolerated in the double-blind phase with the most common side-effects (nausea, headache, insomnia and abnormal dreams) having been well documented in previous trials.
- 16.20. The Committee noted that the 12 week point-prevalence abstinence rate of 64% is much higher than in previous varenicline trials, a difference the authors attribute to the open-label design for the first 12 weeks. The Committee noted that because only those abstinent at week 12 continued to the randomised phase of the trial, the abstinence rates after this time for both varenicline and placebo groups would be expected to be higher than in previous varenicline trials, meaning that patients were more likely to remain abstinent following a second course than patients starting a new quit attempt.
- 16.21. The Committee noted that generalisability of these findings to a real-world New Zealand primary care context is limited by the large number of exclusion criteria, the frequent contact (both face to face and telephone) which provided support and counselling, and the predominantly Caucasian population. The Committee noted that brief interventions in New Zealand GP contexts form only part of a 15 minute consultation, which in general

does not replicate the amount of time, explanation, written consent, support and counselling provided in this clinical trial. The Committee noted that despite counselling being part of the current Special Authority requirements for varenicline, the intensiveness of real world counselling is highly unlikely to be as comprehensive as that seen in this and other clinical trials. The Committee considered that it was highly likely that many patients taking varenicline in New Zealand had one or no counselling sessions.

- 16.22. The Committee noted a recent report of a 24-week trial involving varenicline (Ebbert et al. JAMA 2015;313:687-94). This was a randomised double blind, placebo controlled, multicentre trial in 1510 participants, with a 24-week treatment period and a 28-week follow-up. Participants were not willing/able to make a quit attempt in the next month but were willing to reduce smoking and make a quit attempt in the next three months. Primary efficacy outcome was self-reported, CO-confirmed abstinence for weeks 15-24. Secondary outcomes were abstinence from weeks 21-24 and weeks 21-52.
- 16.23. The Committee considered that the placebo and varenicline groups were well matched, and the participants were more ethnically diverse than the Tonstad et al. (2006) trial. The Committee noted that similar exclusion criteria and frequent contact with counselling advice and support (18 clinic and 10 telephone contacts) applied in this trial, perhaps limiting its generalisability.
- 16.24. For the primary efficacy outcome, 32.1% of the varenicline group had been continuously abstinent from weeks 15-24 vs 6.9% for placebo (RR 4.6, CI 3.5-6.1). From weeks 21-24 the continuous abstinence rate for varenicline was 37.8% vs 12.5% placebo (RR 3.0, CI 2.4-3.7) and for weeks 21-52 the continuous abstinence rate for varenicline was 27% vs 9.9% (RR 2.7, CI 2.1-3.5). The Committee noted that this trial was not designed to compare smoking rates in people taking 24 versus 12 weeks of varenicline. The Committee noted that in previous randomised controlled trials where patients received 12 weeks' varenicline, the continuous abstinence rate during weeks 9-52 was reported as 23% and 21.9% (Jorenby et al., JAMA 2006;296:56-63 and Gonzales et al. JAMA 2006;296:47-55, respectively).
- 16.25. Overall, the Committee considered that there was good quality evidence to suggest that providing an additional 12 weeks' varenicline to people who were abstinent from smoking following an initial 12 weeks' treatment would result in absolute increase in one-year abstinence rates of approximately 6.7%.
- 16.26. The Committee noted that there were a number of other funded smoking cessation treatments: NRT lozenges, patches and gum; bupropion; and nortriptyline, all of which are readily accessible without restrictions and can be used for maintenance treatment.
- 16.27. The Committee noted a study reported by Hays et al. (Ann Intern Med 2001;135:423-33) which was a randomised double-blind, placebo-controlled trial where abstinent patients after 7 weeks of open label bupropion were randomised to 45 weeks of bupropion or placebo as relapse prevention. The continuous abstinence rate was higher for the bupropion group than placebo at week 24 (52.3% vs 42.3%, $p=0.037$) but did not differ between groups after this time.
- 16.28. The Committee noted a systematic review of the effectiveness of relapse prevention interventions among abstinent smokers who had completed an initial course of treatment or who had quit unassisted (Agboola et al. Addiction 2010;105:1362-80). The authors found four randomised controlled trials for bupropion and four for NRT. The analysis reported positive results for the use of these treatments for relapse prevention at 12-18 months: for bupropion the pooled results were OR 1.49; 95% CI 1.10-2.01 NNT 11 and for NRT the pooled results were OR 1.33; 95% CI 1.08-1.63 NNT 20. However, the Committee noted that a Cochrane review of relapse prevention interventions found that extended treatment with bupropion is unlikely to have a clinically important effect and the authors also concluded that studies of extended treatment with NRT are needed (Hajek et

al. Cochrane Database Syst Rev 2013;8:CD0039999). The authors reported that extended treatment with varenicline significantly reduced relapse in one trial (RR 1.18, 95% CI 1.03 to 1.36); pooling of six studies of extended treatment with bupropion failed to detect a significant effect (RR 1.15, 95% CI 0.98 to 1.35); and two small trials of oral NRT failed to detect an effect, but treatment compliance was low, and in two other trials of oral NRT in which short-term abstainers were randomly assigned, a significant effect of intervention was noted.

- 16.29. The Committee noted no evidence was provided to support that maintenance treatment with varenicline would be more effective than using a different pharmacotherapy for maintenance of smoking cessation following an initial 12 weeks' treatment with varenicline. However, the Committee noted that PHARMAC's data show that less than 5% of people who are dispensed 12 weeks' varenicline are prescribed another funded pharmacotherapy within the following month. Therefore, the Committee considered that placebo was an appropriate comparator for this component of the application.
- 16.30. The Committee noted that there is continuing international concern (and monitoring) about the potential for neuropsychiatric side-effects with varenicline. The Committee noted that a Cochrane network meta-analysis (Cahill et al. Cochrane Database Syst Rev 2013;5:CD009329) could not find any trial evidence that varenicline is linked to an increase in neuropsychiatric problems, or with increased heart and circulatory problems. However, the Committee noted that the varenicline trials presented in the application excluded patients with a history of psychiatric illness.
- 16.31. The Committee noted that there was a reasonably high likelihood that, if patients were not assessed in the last week of their first 12-week course, there would be a gap between the first and second 12 weeks of treatment. The Committee considered that unless patients remained abstinent during this time the benefit observed in Tonstad et al. (2006) was unlikely to be realised. The Committee considered that if the patient was not continuously abstinent during the gap then the efficacy would be similar to that observed in patients embarking on a new quit attempt.
- 16.32. The Committee considered that the need for an additional GP consultation in order to be assessed for a maintenance course of varenicline might present a financial barrier for some patients. The Committee noted that this cost would be lower than the cost of cigarettes and that GP costs are generally lower in socio-economically disadvantaged locations.
- 16.33. The Committee noted the supplier's estimate that only 5.7% of patients who receive an initial 12 weeks' varenicline would be dispensed maintenance treatment, based on Australian data. The Committee considered that the proportion in New Zealand would likely be higher than in Australia because of the lower co-payment in New Zealand. The Committee noted that varenicline has some potentially treatment-limiting side effects such as nausea and insomnia, and the need to take the medication twice daily for a further 12 weeks may be off-putting for some patients. The Committee considered that an estimate of up to 20% of patients who receive an initial 12 weeks of varenicline going on to start on a second 12-week course would be more reasonable to use in PHARMAC's analyses; however, the Committee considered it likely that some of these people would not be dispensed a full further 12 weeks.
- 16.34. The Committee considered that there was a reasonably high risk that people who had not completed a full initial 12-week course would seek renewal approvals in order to provide patients with an opportunity to start another (sooner) quit attempt with varenicline. The Committee noted that there would be no mechanism within the Special Authority system to prevent this.
- 16.35. The Committee noted that PHARMAC staff had raised some concerns with the supplier about the modelling of the cost-utility analysis. The Committee agreed that the issues

identified by PHARMAC staff would affect the reported cost-effectiveness of the proposal. The Committee noted PHARMAC staff had engaged with the supplier and that the supplier was open to amending the model.

- 16.36. The Committee considered that if funded access was widened to permit an additional 12 weeks' treatment in patients abstinent after an initial 12 weeks' treatment, clear restrictions would be needed to minimise the large financial risk.
- 16.37. Overall, the Committee considered that there was a small incremental benefit in terms of one-year abstinence rates from an additional 12 weeks' varenicline in people who are abstinent after an initial 12 weeks' varenicline, but use in this way would result in a high financial impact because of the relatively high cost of varenicline. The Committee noted that these patients have access to other, less expensive, smoking cessation pharmacotherapies.

Request to widen access to varenicline by reducing the re-treatment interval from 12 to 6 months

- 16.38. The Committee noted that this request would allow patients to make a new varenicline quit attempt from six months after the start of their previous varenicline quit attempt rather than having to wait until 12 months after the start of their previous attempt. The Committee noted that the supplier provided four key publications in support of this request.
- 16.39. Gonzales et al. (Clin Pharmacol Ther 2014;96:390-6) reported a randomised, double-blind, placebo-controlled, multicentre trial where 498 health adult smokers with one or more previous quit attempt using varenicline for at least two weeks were randomised to 12 weeks' varenicline or placebo with individual counselling. Most (85%) had had just one previous course of varenicline, and two-thirds had had varenicline in the last 12 months. The primary endpoint was continuous abstinence for weeks 9-12 which was 45% varenicline vs 11.8% placebo in the ITT population (OR 7.08, CI 4.34-11.55, $p < 0.0001$); the authors concluded that abstinence rates are comparable with rates reported for varenicline naïve smokers. Discontinuation rates for treatment were approximately 25% and discontinuation rates for the study were 32.1% in the varenicline group and 41.2% in the placebo group. In computing abstinence rates those who discontinued the study were assumed smokers and were included in the denominator. The seven-day point prevalence abstinence rate at week 52 was 28.9% vs 12.2% favouring varenicline (OR 3.06, CI 1.88-4.97, $p < 0.0001$). No new safety signals were reported.
- 16.40. Jorenby et al. (JAMA 2006;296:56-63) reported a phase III, randomised, double-blind, placebo-controlled, multicentre trial where 1027 healthy adults smokers were randomised 1:1:1 to 12 weeks' varenicline, bupropion or placebo plus brief counselling. The primary efficacy outcome was continuous abstinence during weeks 9-12, which was 43.9% in the varenicline group vs. 17.6% in the placebo group (OR 3.85; 95% CI 2.69-5.50; $p < 0.001$) and vs. 29.8% in the bupropion group (OR 1.90, CI 1.38-2.62; $p < 0.001$). For weeks 9-52, the continuous abstinence rates were 23% for varenicline vs 10.3% for placebo (OR, 2.66; 95% CI, 1.72-4.11; $p < 0.001$) and vs 14.6% for bupropion (OR, 1.77; 95% CI, 1.19-2.63; $p = 0.004$). Other secondary endpoints were the 7-day point prevalence abstinence rates at weeks 12 (50.3% vs 20.8% $p < 0.001$ and vs 36.3% $p < 0.001$), 24 (35.2% vs 17.9% $p < 0.001$ and vs 26.3% $p = 0.007$) and 52 (30.5% vs 17.3% $p < 0.001$ and vs 23.4% $p = 0.03$).
- 16.41. Gonzales et al. (JAMA 2006;296:47-55) reported a phase III, randomised, double-blind, parallel-group, placebo and active treatment-controlled, multicentre where 1025 healthy adults smokers were randomised 1:1:1 to 12 weeks' varenicline, bupropion or placebo plus brief counselling. The primary efficacy outcome was continuous four-week abstinence rate during weeks 9-12, which was 44.0% in the varenicline group versus 17.7% in the placebo group (OR 3.85; 95% CI 2.70-5.50; $p < 0.001$) and versus 29.5% in the bupropion group (OR 1.93, CI 1.40-2.68; $p < 0.001$). For weeks 9-52, the continuous abstinence rates were 21.9% for varenicline vs 8.4% for placebo (OR, 3.09; 95% CI, 1.95-

4.91; $p < .001$) and vs 16.1% for bupropion (OR, 1.46; 95% CI, 0.99-2.17; $p = .057$). Other secondary endpoints were the 7-day point prevalence abstinence rates at weeks 12 (50.3% vs 21.2% $p < 0.001$ and vs 35.9% $p < 0.001$), 24 (33.5% vs 14.5% $p < 0.001$ and vs 24.9% $p = 0.01$) and 52 (28.1% vs 14% $p < 0.001$ and vs 22.8% $p = 0.13$).

- 16.42. Aubin et al. (Thorax 2008;63:717-24) reported a phase III, randomised, multi-centre open-label trial comparing 12 weeks' varenicline and 10 weeks' nicotine patch with down-titration of the nicotine dose with time. A total of 746 participants randomised to take either nicotine patch or varenicline and were followed for 52 wk. The primary outcome was continuous abstinence rate for the last four weeks of treatment (55.9% for varenicline and 43.2% for nicotine patch, OR 1.7; 95% CI 1.26-2.28; $p < 0.001$). Secondary outcomes were continuous abstinence for the last four weeks of treatment at 24 weeks (no statistically significant difference for the primary analysis population) and 52 weeks (no statistically significant difference for the primary analysis population). For the all-randomised analysis, incremental quit rates for varenicline compared with nicotine patch at week 52 were 6.1% which did reach statistical significance. The 7-day point prevalence abstinence rates showed similar patterns at weeks 12, 24 and 52 with a difference favouring varenicline at week 12, but no significant difference at weeks 24 and 52. The Committee considered that key limitations of this trial include its open label design and longer duration of treatment with varenicline.
- 16.43. The Committee noted that only the Gonzales 2014 trial described above was designed to include patients who had a prior quit attempt with varenicline, and the quit rates in this trial were similar to that seen in the other randomised controlled varenicline trials provided. The Committee considered that in this patient population it would be reasonable to assume similar efficacy rates for varenicline as for patients who had not had a previous quit attempt with varenicline.
- 16.44. The Committee noted the Cochrane network meta-analysis indirect comparison (Cahill et al. Cochrane Database Syst Rev 2013;5:CD009329) which reported comparisons between bupropion and NRT suggested equal efficacy (OR 0.99, 95% CI 0.86-1.13) and that varenicline was superior to single forms of NRT (OR 1.57, 95% CI 1.29-1.91) and to bupropion (OR 1.59, 95% CI 1.29-1.96), but varenicline was not more effective than combination NRT (OR 1.06, 95%CI 0.75-1.48).
- 16.45. The Committee noted a recent publication by Baker et al. 2016 (JAMA 2016;315:371-9), which reported an open-label randomised controlled trial comparing effects of nicotine patch, varenicline and combination NRT on smoking cessation. The head-to-head study found no significant differences in any abstinence outcome at 26 weeks and 52 weeks. The Committee noted that, taking into account the limitations inherent in its open label design, this trial suggests pharmacologically supported quit attempts in general are important in smoking cessation rather than the specific individual smoking cessation pharmacotherapies.
- 16.46. The Committee noted that there was no evidence provided to suggest that patients who have had a previous varenicline quit attempt are more likely to be successful if their next quit attempt is with varenicline compared to one of the other funded smoking cessation treatments. As previously the Committee noted that there were currently no particular problems with access to the alternative treatments. In this respect, the Committee noted that varenicline would be of most benefit in patients who are intolerant to other treatments or unwilling to try them again.
- 16.47. The Committee noted that approximately 30% of funded varenicline use currently was for people who had had at least one previous quit attempt with varenicline. The Committee disagreed with the supplier's estimate that approximately 19% of people who have used varenicline would take varenicline again within 6-12 months of the previous attempt if this was permitted by the funding rules; the Committee considered it likely that this would occur in up to 50% of patients. The Committee noted that this would be associated with a

very high budgetary risk when compared with the cost of quit attempts with other funded treatments.

- 16.48. The Committee noted that, depending on how long after a Special Authority approval was granted the patient embarked on their quit attempt, it would be possible for patients to embark on two quit attempts in quick succession if the request to shorten the renewal interval was progressed.
- 16.49. The Committee considered that in the real world setting there was likely to be little difference between the available pharmacotherapies for smoking cessation; however, if the availability of varenicline within 6-12 months of an initial quit attempt did result in more patients embarking on another quit attempt then this would likely result in increased successful quit attempts as each supported quit attempt is an opportunity to successfully stop smoking.

Request to replace the current two-week 'starter' and 'follow-on' packs of varenicline with a four-week 'initiation' pack

- 16.50. The Committee noted that varenicline is currently supplied as a two-week starter pack (0.5 mg x 11 tablets and 1 mg x 14 tablets), a two-week follow-on pack (1 mg x 28 tablets) and a four-week continuation pack (1 mg x 56 tablets). The Committee noted that the supplier has proposed that the two-week starter pack and the two-week follow-on pack be replaced by a four-week initiation pack (0.5 mg x 11 tablets and 1 mg x 42 tablets).
- 16.51. The Committee considered that, based on current prescribing and dispensing patterns, this change would be unlikely to increase the proportion of people starting on varenicline who would complete a 12-week course of varenicline.
- 16.52. The Committee considered that there appeared to be no particular clinical benefit from the proposed change, so any change would need to be cost-neutral to the current funding situation. The Committee noted and agreed with PHARMAC staff assessment of where potential costs and savings would occur based on current prescribing and dispensing patterns.