

PTAC meeting held on 11 & 12 August 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 2016*.

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

Cardiovascular Subcommittee

- 1.1. The Committee noted and reviewed the minutes from the Cardiovascular Subcommittee meeting of 17 February 2016, and accepted the recommendations related to items 3, 4, 5, 8 and 10.
- 1.2. Regarding item 6, Eplerenone, the Committee noted that following PTAC's request, the Cardiovascular Subcommittee had reviewed the application for eplerenone in patients with heart failure who are intolerant to optimal dosing of spironolactone.
- 1.3. The Committee noted that at its November 2015 meeting, PTAC requested that the Cardiovascular Subcommittee review the application to examine the strength of the evidence and to determine appropriate Special Authority criteria. The Committee noted that the Subcommittee had subsequently recommended that eplerenone be funded with a high priority in patients with an ejection fraction of less than 40% and who suffer from severe disabling mastalgia. The Committee disagreed with the Subcommittee's recommendation and declined to ratify recommendation 6.2.
- 1.4. With respect to section 6.2, the Committee noted the Subcommittee's restriction of eplerenone to patients with heart failure with an ejection fraction of less than 40% and considered that this was reasonable. However, the Committee considered that the definition of 'mastalgia' is not well understood and that the group of patients who prescribers would consider to have severe, disabling mastalgia would be large, despite few patients actually suffering from severe, disabling mastalgia as a side effect of spironolactone. The Committee considered that its November 2015 recommendation, of low priority, for funding eplerenone for patients with heart failure who are intolerant to optimal dosing of spironolactone should remain. However, members considered that the degree of heart failure should be quantified, and that this recommendation should be for patients with heart failure and an ejection fraction of less than 40%.
- 1.5. In addition, regarding item 6, eplerenone, the Committee noted that the Cardiovascular Subcommittee also reviewed the application for eplerenone in patients with an ejection fraction of less than or equal to 40% and diabetes, or a high risk of diabetes and had deferred making a recommendation until the results of the Montreal SNOW trial are available. The Committee noted this deferral of recommendation and requested that the Montreal SNOW trial be brought to PTAC for review once it is published.
- 1.6. Regarding item 7, fixed dose combination polypills, the Committee noted that the Cardiovascular Subcommittee had reviewed an application by PHARMAC staff on the broader issue of fixed dose combination polypills for the management of cardiovascular risk. The Committee noted that as part of this discussion, the Te Arai Biopharma submission for the Trinomia polypill was reviewed in its entirety. The Committee noted that the evidence presented did not include any randomised control trials of the particular product that reported cardiovascular outcomes.
- 1.7. The Committee considered that it would not be willing to consider applications for fixed dose combination pills that cited evidence with surrogate outcome measures. The Committee considered that, before considering this issue again, robust evidence in the form of good quality, well-designed trials with hard cardiovascular outcomes would be needed. The Committee considered that it would be appropriate for the Cardiovascular Subcommittee to consider any new evidence in the first instance. The Committee requested that recommendations made by the Subcommittee regarding this new evidence then be presented to PTAC for its further consideration in addition to the full application.

Cancer Treatments Subcommittee

- 1.8. The Committee noted the minutes from the Cancer Treatments Subcommittee (CaTSoP) meeting of 22 April 2016, and accepted recommendations related to items 1, 2, 3, 4, 7, 9, 11, and 12.
- 1.9. Regarding item 5, Therapeutic Group review and NPPA review, the Committee noted there was uncertainty regarding the potential patient numbers and therefore fiscal risk of widening access to rituximab for hairy cell leukaemia. The Committee noted that this would be further considered by CaTSoP at their next meeting and requested that the minute of this discussion be reviewed by PTAC prior to progressing the funding application. The Committee noted and agreed with the remainder of item 5.
- 1.10. Regarding item 6, lenalidomide review, the Committee considered the recommended amendments to the current Special Authority detailed in 6.10 were reasonable. However, the Committee considered that the recommended widening of access to first-line treatment for patients with grade 3 or greater pre-existing peripheral neuropathy may represent a significant change to the currently funded population depending on interpretation of severe peripheral neuropathy and could represent a significant fiscal risk. The Committee considered that funding for this population should be considered via NPPA if patient numbers were expected to be small.
- 1.11. Regarding item 8, dabrafenib and trametinib for BRAF v600 metastatic melanoma, the Committee noted that the Subcommittee had recommended funding with a high priority based on the high health need of the population and in the absence of other funded treatments for advanced melanoma.
- 1.12. The Committee noted that subsequent to the Subcommittee's consideration of this treatment, the decision to fund nivolumab and pembrolizumab for the treatment of advanced melanoma had been made. The Committee noted that it was unclear what the Subcommittee's recommendation would be now that two treatments were funded for advanced melanoma patients.
- 1.13. The Committee considered that the funding of BRAF inhibitors should be reconsidered in the light the new treatment landscape for patients with advanced melanoma.
- 1.14. The Committee reiterated its recommendation that the application for dabrafenib in combination with trametinib for BRAF v600 mutation positive advanced melanoma be declined noting the associated toxicity, uncertainty regarding magnitude and duration of benefit, the high cost, and recent funding of PD-1 inhibitors for this patient population.
- 1.15. Regarding item 10, ipilimumab monotherapy for previously treated and unresectable stage IIIc and IV melanoma, the Committee noted the Subcommittee had recommended funding with medium priority in the absence of other funded melanoma treatments but that from 1 September 2016 two treatments for advanced melanoma would be funded.
- 1.16. The Committee reiterated its recommendation that ipilimumab as monotherapy be funded with low priority for patients with the funding application for patients with previously treated unresectable stage IIIc or IV melanoma.
- 1.17. Regarding item 13, nivolumab for locally advanced or metastatic squamous and non-squamous non-small cell lung cancer (NSCLC), the Committee noted and agreed with the minute except for the priority of the Subcommittee's recommendations; noting in particular the immaturity of the data.
- 1.18. The Committee noted that the subgroup of patients with EGFR positive NSCLC was not specifically considered by PTAC but considered it reasonable to fund nivolumab for this patient population as a third-line treatment following both platinum-based chemotherapy and erlotinib or gefitinib, with a low priority.

- 1.19. The Committee recommended that nivolumab as monotherapy be funded for the treatment of patients with locally advanced or metastatic squamous NSCLC that has progressed on or after prior platinum-based chemotherapy with low priority.
- 1.20. The Committee recommended that nivolumab as monotherapy be funded with a low priority for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC that has progressed on or after prior platinum-based chemotherapy.
- 1.21. The Committee recommended that nivolumab as monotherapy be funded with a low priority for the treatment of patients with EGFR mutation positive locally advanced or metastatic nonsquamous NSCLC that has progressed after both prior platinum-based chemotherapy and erlotinib or gefitinib.
- 1.22. Regarding item 14, crizotinib for acute lymphoblastic leukemia (ALL), The Committee noted and agreed with the minute related to this item, except for the definition of allergy and the patient population.
- 1.23. The Committee considered that patients who develop an allergy to L-asparaginase or pegaspargase could still receive some benefit from further treatment with these agents.
- 1.24. The Committee noted that the definition allergy in relation to the use of L-asparaginase or pegaspargase, such that further treatment was contraindicated, was not robustly outlined, and considered that documentation of severe allergy should be required for funded access to crizotinib and that an appropriate definition of allergy could be that 'L-asparaginase or pegaspargase are contraindicated or ineffective'.
- 1.25. The Committee considered the evidence to be of moderate strength and quality for the treatment of ALL. The Committee also considered that there was a spectrum of other malignancies for which L-asparaginase was used in a curative setting and, given the biological similarity to ALL, it was reasonable to consider they could respond to crizotinib in the same way. The Committee considered that crizotinib should not be used in a palliative setting.

Cancer Treatments Subcommittee

- 1.26. The Committee noted the minutes from the Cancer Treatments Subcommittee (CaTSOP) teleconference of 20 May 2016, and agreed with the minute regarding item 2, ibrutinib for chronic lymphocytic leukemia and mantle cell lymphoma, except for priority of the Subcommittee's recommendations, noting uncertainty regarding the overall survival benefit from treatment with ibrutinib.
- 1.27. The Committee recommended that ibrutinib be funded with a low priority for the treatment of CLL with chromosome del(17p) or TP53 mutation at diagnosis or relapse.
- 1.28. The Committee recommended that ibrutinib be funded with a low priority for the treatment of relapsed CLL (within 24 months of prior therapy).
- 1.29. The Committee recommended that ibrutinib be funded with a low priority for the treatment of refractory CLL (progressed within 12 months).
- 1.30. The Committee recommended that ibrutinib be funded with a low priority for the treatment of relapsed and/or refractory MCL (that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy).
- 1.31. The Committee considered that the application should be further considered once the RESONATE-17 study had been published.
- 1.32. The Committee noted and agreed with the minute regarding item 3, crizotinib for ALK-positive advanced and/or metastatic NSCLC, except for the priority of the Subcommittee's

recommendations some trial design issues, lack of evidence of long term efficacy, and poor cost effectiveness at the proposed price.

- 1.33. The Committee reiterated its recommendations that crizotinib as a first and second line treatment for ALK positive advanced and metastatic NSCLC be declined.

Gaucher Panel

- 1.34. The Committee noted the minutes from the Gaucher Panel meeting in June 2016 were not yet finalised, however a verbal summary of the discussion was provided by PHARMAC staff. The Committee noted the Gaucher Panel considered there is no clinical reason not to run a competitive process, such as an RFP, for a first-line enzyme-replacement therapy for Gaucher disease and that it would be possible to switch all existing patients from imiglucerase to velaglucerase alfa if necessary, including any patients with type 3 Gaucher disease. The Gaucher Panel provided detailed advice regarding how a potential product change could be managed. The Committee considered that it was satisfied with the advice from the Panel and there was no need to circulate the minutes further. The Committee noted PHARMAC staff would continue with planning for a competitive process and would provide an update to the Committee at the next PTAC meeting.

2. Correspondence

Simeprevir

- 2.1. The Committee noted correspondence from Janssen-Cilag Ltd in response to PTAC's February 2016 meeting minutes for simeprevir (Olysio) for the treatment of chronic hepatitis C.
- 2.2. The Committee noted the comments from Janssen-Cilag in relation to minute 7.18:
- 2.3. "The Committee noted that simeprevir, as with other protease inhibitors, would be contraindicated in patients with decompensated cirrhosis and that there would be a need for another agent to treat patients with severe liver disease."
- 2.4. These comments included the contention that only boceprevir is contraindicated in patients with decompensated cirrhosis and that simeprevir (Olysio) and telaprevir (Incivo) are not contraindicated, although caution is advised in the use of these agents.
- 2.5. The Committee considered that this minute should be amended to reflect this point as follows (additions in bold, deletions in strikethrough):

~~"The Committee noted that simeprevir as with other protease inhibitors, would be contraindicated in patients with decompensated cirrhosis and~~ **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> **updated July 2016**). **The Committee considered** that there would be a need for another agent to treat patients with severe liver disease."
- 2.6. The Committee thanked Janssen-Cilag for its comments.
- 2.7. The Committee considered the information provided does not change its previous recommendation that simeprevir (Olysio) should be funded for the treatment of chronic hepatitis C genotype 1 infection if cost-neutral to boceprevir.

3. Enzalutamide for the treatment of metastatic castration-resistant prostate cancer

Application

- 3.1. The Committee reviewed a funding application from Seqirus (NZ) Ltd for the listing of enzalutamide for the treatment of patients with metastatic castration-resistant prostate cancer.

Recommendation

- 3.2. The Committee **recommended** that enzalutamide be listed on the Pharmaceutical Schedule for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), but only if cost-neutral compared with the comparator treatment option abiraterone.

- 3.3. The Committee **recommended** that enzalutamide be listed subject to the same Special Authority criteria as abiraterone for the treatment of mCRPC as follows:

Special Authority for Subsidy

Initial Application only from a Medical Oncologist, Radiation Oncologist or Urologist or any other medical practitioner on the recommendation of a Medical Oncologist, Radiation Oncologist or Urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1. Patient has prostate cancer; and
2. Patient has metastases; and
3. Patient's disease is castration resistant; and
4. Any of the following:
 - 4.1. All of the following:
 - 4.1.1. Patient is symptomatic; and
 - 4.1.2. Patient has disease progression (rising serum PSA) after second line anti-androgen therapy; and
 - 4.1.3. Patient has ECOG performance score of 0-1; and
 - 4.1.4. Patient has not had prior treatment with taxane chemotherapy; and
 - 4.1.5. Patient has not had prior treatment with abiraterone; or
 - 4.2. All of the following:
 - 4.2.1. Patient's disease has progressed following prior chemotherapy containing a taxane; and
 - 4.2.2. Patient has ECOG performance score of 0-2; and
 - 4.2.3. Patient has not had prior treatment with abiraterone; or
 - 4.3. Both:
 - 4.3.1. The patient has discontinued abiraterone within 3 months of starting treatment due to intolerance; and
 - 4.3.2. The cancer did not progress whilst on abiraterone; and
5. Enzalutamide to be administered as monotherapy; and
6. Patient's disease has not progressed following previous treatment with enzalutamide.

Renewal only from a Medical Oncologist, Radiation Oncologist or Urologist or any other medical practitioner on the recommendation of a Medical Oncologist, Radiation Oncologist or Urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1. Significant decrease in serum PSA from baseline; and
2. No evidence of clinical disease progression; and
3. Enzalutamide to be administered as monotherapy; and
4. The treatment remains appropriate and the patient is benefiting from treatment.

- 3.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 3.5. The Committee noted that the supplier had applied for funding of enzalutamide for the treatment of patients with mCRPC in both the clinical situations of; chemotherapy naïve, and who have previously received docetaxel.
- 3.6. The Committee noted that prostate cancer is both the most commonly-diagnosed form of cancer in New Zealand men and in New Zealand overall. The Committee noted that mortality rates for Māori were higher than for non-Māori.
- 3.7. The Committee noted that first line treatment for prostate cancer is androgen deprivation therapy, also known as medical-castration, comprising suppression of testosterone production from the testes with gonadotropin-releasing hormone (GnRH) agonists, an alternative to which is surgery, and testosterone blockade with agents such as flutamide and bicalutamide.
- 3.8. The Committee noted that prostate cancer has a variable disease course but eventually becomes castrate-resistant which presents as one or any combination of a continuous rise in serum levels of prostate-specific antigen, progression of pre-existing disease, or appearance of new metastases despite androgen deprivation therapy.
- 3.9. The Committee noted that abiraterone is currently funded for the treatment of mCRPC for patients who are taxane naïve, and in patients who have received prior chemotherapy containing a taxane.
- 3.10. The Committee noted that enzalutamide is an orally administered androgen receptor antagonist that competitively inhibits binding of androgens to androgen receptors in the androgen receptor signalling pathway thereby inhibiting the nuclear translocation of these receptors, DNA binding, and coactivator recruitment.
- 3.11. The Committee noted that enzalutamide has a different mechanism of action to abiraterone which selectively inhibits the enzyme 17 α -hydroxylase/ C17.20-lyase (CYP17), an enzyme which is expressed in testicular, adrenal, and prostatic tumour tissues.
- 3.12. The Committee noted that the key evidence for the use of enzalutamide in the treatment of mCRPC is from two phase III trials: AFFIRM as a second-line and PREVAIL as a first-line treatment.

Second-line treatment

- 3.13. The Committee noted that the AFFIRM study (Scher et al. NEJM 2012;367:1187-97) was a phase III, double-blind, randomised, placebo-controlled trial in 1199 patients with castration-resistant prostate cancer who have been previously treated with one or two chemotherapy regimens, at least one of which contained docetaxel. The Committee noted that patients were randomly assigned 2:1 to receive either enzalutamide (160 mg daily, n=800) or matched placebo (n=399) until radiographically confirmed disease progression requiring initiation of new systemic antineoplastic therapy.
- 3.14. The Committee noted that eligibility criteria included castrate levels of testosterone (<50 ng per decilitre) and progressive disease defined according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria including three increasing values for prostate specific antigen (PSA) or radiographically confirmed progression with or without a rise in PSA level.
- 3.15. The Committee noted that at a median follow-up of 14.4 months pre-planned interim analysis was conducted, median overall survival (OS), the primary endpoint of the study was reported to be 18.4 months (95% CI, 17.3 to not reached) for the enzalutamide arm and 13.6 months (95% CI, 11.3-15.8) for the placebo arm with a 37% reduction in the

risk of death for the enzalutamide arm compared to the placebo arm (HR 0.63; 95% CI, 0.53 to 0.75; $p < 0.001$).

- 3.16. The Committee noted that on the basis of these results the study was halted and unblinded, with eligible patients in the placebo group offered treatment with enzalutamide; 29% of patients in the enzalutamide arm were receiving study drug and 5% in the placebo arm.
- 3.17. The Committee noted that radiographic progression-free survival (PFS), a secondary endpoint, was 8.3 months in the enzalutamide arm versus 2.9 months in the placebo arm (hazard ratio, 0.40; $P < 0.001$).
- 3.18. The Committee noted that secondary endpoints also included quality of life response defined as a 10-point improvement in the global score on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart. The Committee noted that FACT-P quality-of-life response was reported to be 43% in the enzalutamide arm compared to 18% with placebo ($P < 0.001$).
- 3.19. The Committee noted that adverse events of \geq grade 3 were reported in 45% of patients in the enzalutamide arm compared with 53% of patients in the placebo arm.

First-line treatment

- 3.20. The Committee noted that the PREVAIL study (Beer et al. NEJM 2014;371:424-33) was a phase III, double-blind, randomised, placebo-controlled trial in 1717 chemotherapy naïve patients with histologically or cytologically confirmed adenocarcinoma of the prostate with documented metastases.
- 3.21. The Committee noted that patients were randomly assigned 1:1 to receive either enzalutamide (160 mg daily, $n=872$) or matched placebo ($n=845$) until unacceptable side effects or confirmed radiographic progression and the initiation of chemotherapy or an investigational agent.
- 3.22. The Committee noted that eligibility criteria included no previous treatment with cytotoxic chemotherapy, ketoconazole, or abiraterone acetate, PSA progression, radiographic progression or both in bone or soft tissue despite receiving LHRH analogue therapy or undergoing orchiectomy with a serum testosterone level of < 50 ng per decilitre. The Committee noted that continued androgen-deprivation therapy was required and previous antiandrogen therapy and concurrent use of glucocorticoids were permitted but not required.
- 3.23. The Committee noted that at the planned interim analysis with median duration of follow-up of 22 months, median OS was estimated at 32.4 months in the enzalutamide group compared with 30.2 months in the placebo group. In the enzalutamide group 28% of patients had died compared with 35% in the placebo group (HR 0.71; 95% CI, 0.60-0.84; $p < 0.001$). The Committee noted an updated OS analysis following an additional 116 deaths showed 82% of patients in the enzalutamide group and 73% in the placebo group were alive at 18 months. The Committee noted that cross over of the survival curves occurs at approximately 32 months.
- 3.24. The Committee noted that at 12 months of follow-up, the rate of radiographic PFS was 65% in the enzalutamide arm and 14% in the placebo arm and that the median radiographic PFS was not reached in the enzalutamide arm, as compared with 3.9 months in the placebo arm.
- 3.25. The Committee noted that subsequent antineoplastic treatments were received by 40% of patients in the enzalutamide group compared with 70% in the placebo group (docetaxel 33% and 57% respectively and abiraterone 21% and 46% respectively).

- 3.26. The Committee noted that adverse events of \geq grade 3 were reported in 43% in the enzalutamide group compared with 37% of the placebo group.

General comments

- 3.27. The Committee considered that the evidence to support the use of enzalutamide in mCRPC was of good strength and quality and of relevance to the New Zealand setting. The Committee considered that reasonable evidence was provided for quality of life data for treatment-naïve mCRPC patients.
- 3.28. The Committee considered that based on the currently available evidence pre-treated mCRPC patients are likely to benefit more from treatment with enzalutamide in terms of OS and quality of life than patients who are treatment naïve.
- 3.29. The Committee noted that enzalutamide has no dietary restrictions with dosing regimen, and has reduced liver function monitoring requirements and reduced steroid use when compared with abiraterone. However, the Committee considered these benefits were difficult to quantify and likely minimal and that any improvements when compared with abiraterone were unlikely to be clinically meaningful or cost-saving.
- 3.30. The Committee considered that while there were currently no head-to-head trials comparing abiraterone with enzalutamide, and taking into account different drug interaction profiles, it was reasonable to consider them clinically equivalent in the treatment of mCRPC. However, the Committee considered that because of their different mechanism of action it would not be appropriate to run a commercial process resulting in only one of these agents being funded.
- 3.31. The Committee considered in future it was possible that enzalutamide and abiraterone may be used sequentially and as combination treatments but the evidence did not currently support this approach. Members noted that sequencing and combination trials were currently being undertaken.
- 3.32. The Committee considered that currently enzalutamide and abiraterone were used following androgen deprivation therapy but treatment paradigms for mCRPC were not settled. The Committee considered it was likely clinical practice in future would look to use these agents earlier in the treatment paradigm.

4. Brentuximab vedotin for patients with relapsed or refractory CD30 + lymphoma

Application

- 4.1. The Committee considered an application from a clinician for the funding of brentuximab vedotin for the following indications:
- Relapsed refractory Hodgkin's lymphoma (HL) after 2 or more cycles of chemotherapy and ineligible for autologous stem cell transplant (auto-SCT);
 - Relapsed refractory HL after auto-SCT;
 - Relapsed refractory HL after allogeneic stem cell transplant (allo-SCT); and
 - Relapsed refractory systemic anaplastic large cell lymphoma (sALCL).
- 4.2. The Committee also considered a number of published studies provided by PHARMAC staff for the use of brentuximab vedotin in the treatment of CD30+ lymphomas.

Recommendation

- 4.3. The Committee **recommended** the application for brentuximab vedotin for the treatment of relapsed refractory HL, after 2 or more cycles of chemotherapy and ineligible for auto-SCT be declined.

- 4.4. The Committee **recommended** that the application brentuximab vedotin for the treatment of patients with relapsed refractory HL prior to auto-SCT be declined.
- 4.5. The Committee **recommended** that brentuximab vedotin for the treatment of relapsed refractory HL after auto-SCT as a bridge to allo-SCT, be funded with low priority.
- 4.6. The Committee **recommended** the application for brentuximab vedotin for the treatment of relapsed refractory HL after auto-SCT and not as a bridge to allo-SCT be declined.
- 4.7. The Committee **recommended** the application for brentuximab vedotin for the treatment of relapsed refractory HL after allo-SCT be declined.
- 4.8. The Committee **recommended** that brentuximab vedotin for children with relapsed refractory sALCL after auto-SCT as a bridge to allo-SCT, be funded with low priority.
- 4.9. The Committee **recommended** the application for brentuximab vedotin for the treatment of relapsed refractory sALCL be deferred pending publication of the ECHELON-2 trial.
- 4.10. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for advice regarding how to define patients who are eligible for SCT and development of Special Authority criteria.
- 4.11. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 4.12. The Committee noted the two main forms of lymphoma are HL and Non-Hodgkin's lymphoma (NHL) and that around 5% of adult NHL and up to 30% of paediatric NHL are sALCL, a subtype of T-cell lymphoma.
- 4.13. The Committee noted that HL and sALCL affect approximately twice as many men than women and has a bimodal age distribution with peaks in childhood/young adulthood and again in late adulthood.
- 4.14. The Committee noted that studies report 80% of patients with HL achieve long term progression free survival and 5 year survival rates of 98% with first-line chemotherapy/radiotherapy regimes. The Committee noted that high levels of remission are also achieved with second-line chemotherapy agents for patients with relapsed or refractory disease.
- 4.15. The Committee noted reports that a good level of response is generally achieved with auto-SCT but up to 50% of HL patients relapse following auto-SCT with median overall survival (OS) of 40.5 months. The Committee noted that relapse rates for patients with sALCL are generally higher than those seen in HL.
- 4.16. The Committee noted that PHARMAC has received a number of Named Patient Pharmaceutical Assessment applications for brentuximab vedotin for patients with relapsed refractory HL and sALCL at various disease stages including: following previous chemotherapy treatment as bridge to auto-SCT or tandem auto/allo-SCT, and following auto-SCT as monotherapy or as bridging to allo-SCT.
- 4.17. The Committee noted that there are over 100 clinical studies underway investigating the use of brentuximab vedotin in lymphoma and various other indications.

Relapsed refractory HL before auto-SCT

- 4.18. The Committee considered evidence for the use of brentuximab vedotin from a post hoc analysis in 20 transplant-naïve patients with HL enrolled in two single arm, open-label, dose escalation, phase I studies of brentuximab administered every 3 weeks or every

week for 3 out of every 4 weeks (Forero-Torres et al. *The Oncologist* 2012;17:1073-80). Eligibility criteria included patients for whom systemic chemotherapy as induction had failed and who were ineligible for or had refused treatment with auto-SCT.

- 4.19. The Committee noted that six patients obtained an objective response (OR), including two with complete response (CR) and four with partial response (PR), while ten patients were stable, two had progression, and two patients were reported as early discontinuations.
- 4.20. The Committee noted that there was a wide variation in dose (0.1-2.7mg/kg) and duration of treatment (3.0-51.9 weeks) and considered there appeared to be no correlation between dose or schedule of treatment and outcome. The Committee noted that 3 of 6 responders who had previously been ineligible for auto-SCT became eligible after treatment with brentuximab vedotin.

Relapsed refractory HL after auto-SCT

- 4.21. The Committee reviewed evidence from the pivotal, open-label, single arm, phase II trial of brentuximab vedotin (1.8mg/kg every three weeks for a maximum of 16 cycles) in 102 patients with relapsed refractory HL post auto-SCT (Younes et al. *J Clin Onc.* 2012;30:2183-9; Gopal et al. *Blood.* 2015;125:1236-43).
- 4.22. The Committee noted that at a median follow-up of 33.3 months, the objective response rate, being the primary endpoint of the study, was 75% (95% CI, 65-83%).
- 4.23. The Committee noted that 34% (95% CI, 25-44%) of all patients achieved CR and after a median of 53.3 months follow-up 16 patients remained progression-free and 12 patients had not received consolidative allo-SCT.
- 4.24. The Committee noted that for patients who had an OR, the median duration of response was 6.7 months and for those who achieved CR median duration of response was 20.5 months (95% CI, 10.8-not estimable).
- 4.25. The Committee reviewed evidence from a retrospective analysis of data from consecutive case series of 18 patients with HL expressing CD30 who received brentuximab vedotin prior to reduced-intensity allo-SCT of which 17 had received prior auto-SCT (Chen et al. *Blood* 2012;119:6379-81). The Committee noted that median follow-up after allo-SCT was 14.0 months (range 1.7-22.9) and that 16 patients were progression-free and 2 patients were in relapse.
- 4.26. The Committee reviewed evidence from the AETHERA study – a randomised, double blind, placebo-controlled, phase III trial of brentuximab vedotin in 329 patients with unfavourable-risk relapsed or primary refractory classic HL who had undergone high-dose chemotherapy and auto-SCT (Moskowitz et al. *Lancet* 2015;385:1853-62). The Committee noted that patients were randomised 1:1 to receive 16 cycles of 1.8 mg/kg brentuximab vedotin (n=165) or placebo (n=164) on day 1 of each 21 day cycle or placebo, starting 30-45 days after transplantation.
- 4.27. The Committee noted that eligibility criteria included: relapsed HL with initial remission duration of less than 12 months; CR, PR, or stable disease after pre-transplantation salvage chemotherapy; and no previous treatment with brentuximab vedotin.
- 4.28. The Committee noted that patients with disease progression were unblinded and patients in the placebo arm could receive brentuximab treatment. The Committee noted that 85 patients received subsequent treatments after progression of which 72 patients received brentuximab.
- 4.29. The Committee noted that at a median follow-up of 30 months the median progression-free survival (PFS), the primary study endpoint, was 42.9 months in the brentuximab arm (95% CI, 30.4 – 42.9) and 24.1 months in the placebo arm (11.5 – not estimable).

The Committee noted that 23 patients in the brentuximab arm and 12 patients in the placebo arm proceeded to allo-SCT.

- 4.30. The Committee noted that 32% of patients in the brentuximab arm had dose reductions because of adverse events compared to 3% in the placebo arm. The Committee noted that adverse events in the brentuximab arm included neutropenia, upper respiratory tract infection and fatigue, with peripheral sensory neuropathy being the most common adverse event of any grade.

Relapsed refractory HL after allo-SCT

- 4.31. The Committee noted evidence for the safety and efficacy of brentuximab vedotin in 25 patients with HL with relapsed, refractory or progressive disease after at least 1 prior systemic chemotherapy and allo-SCT (Gopal et al. 2012 Blood;120:560-8).
- 4.32. The Committee noted that exclusion criteria included allo-SCT within 100 days or auto-SCT within 4 weeks, concurrent therapy with corticosteroids, low neutrophil or platelets, or an Eastern Cooperative Oncology Group (ECOG) performance status of >1. The Committee noted that eligible patients had received a median of 9 prior treatment regimens (5-19) with 76% of patients having had prior auto-SCT.
- 4.33. The Committee noted that patients were treated as part of three open-label, non-randomised trials with brentuximab vedotin either 1.2 mg/kg (n=6) or 1.8 mg/kg (n=19) every three weeks until progression or toxicity.
- 4.34. The Committee noted that patients received a median of 8 cycles (1-16) over median treatment duration of 27.4 weeks (2.1-53.1) and that at the time of data cut-off, 6 patients remained on treatment, 8 had discontinued due to disease progression and 9 due to adverse events.
- 4.35. The Committee noted 12 patients (50%) had an OR, including 9 (38%) with CR and 3 (13%) with PR, 10 patients (42%) had stable disease and 2 patients (8%) had disease progression. The Committee noted that with a median follow up to 34 weeks, median PFS for all patients was 7.8 months (0.5-12.2+) and the median OS had not been reached as 23 patients remained alive.
- 4.36. The Committee noted that all patients experienced at least 1 adverse event with 72% of patients experiencing at least one adverse event of \geq grade 3 with neutropenia, anaemia and thrombocytopenia and hyperglycemia reported in more than 2 patients.
- 4.37. The Committee also reviewed a retrospective evaluation of brentuximab vedotin (1.8 mg/kg every 3 weeks for a maximum of 16 cycles) in 16 patients with relapsed refractory HL and a failed allo-SCT (Carlos-Stella et al. Oncologist. 2015;2:323-8). The Committee noted that at a median follow up of 26 months, objective response rate was 69%, median PFS was 7 months, median OS was 25 months and median duration of response was 5 months. The Committee noted that median treatment duration was 6 months (2-14) and that best response was achieved after a median of 4 cycles (2-12) including 31% CR, 37% PR with 25% stable disease and 6% progressive disease.

Relapsed refractory sALCL

- 4.38. The Committee reviewed evidence for the use of brentuximab vedotin (1.8 mg/kg every 3 weeks for up to 16 doses) for the treatment of relapsed refractory sALCL after treatment failure with at least one prior line of therapy (Pro et al. J of Clin Onc. 2012. 30; 2183-97). The Committee noted that eligibility criteria included and ECOG status of 0 or 1 and had not received prior allo-ST.
- 4.39. The Committee noted that objective response, the primary endpoint, was achieved in 50 out of 58 patients (86%;95% CI 75-94%) including 57% CR and 29% PR and the median duration of OR was 12.6 months. The Committee noted that 6 patients that had

achieved CR had subsequent allo-SCT and 5 patients in CR had subsequent auto-SCT with a median duration of OR of 13.2 months and not reached respectively. The Committee noted that 22 patients that achieved CR did not receive subsequent SCT with a mean duration of OR of 12.6 months.

- 4.40. The Committee noted that grade 3 or greater adverse events that were reported in more than 10% of patients including neutropenia, thrombocytopenia and peripheral sensory neuropathy.
- 4.41. The Committee reviewed evidence from three-year survival results from an ongoing phase II study of brentuximab vedotin (1.8 mg/kg every 3 weeks for up to 16 cycles) in 58 patients with relapsed or refractory sALCL (Advani et al. Blood. 2013;122:1809).
- 4.42. The Committee noted that after a median follow up of 33.4 months, the median duration of response at 13.2 months (5.7-26.3) and median duration of response if CR was 26.3 months (13.2-NE). The Committee noted that at the time of analysis, those patients who achieved CR, 47% remained in remission and 64% remained alive.
- 4.43. The Committee noted that 29% of patients that achieved CR received SCT (1:1 auto:allo-SCT), and the median PFS for patients with CR with SCT was not yet met compared to 18.4 months (8.4-33.7) without SCT.
- 4.44. The Committee noted that median PFS for all patients was 14.6 months and median OS was not reached and the estimated 3-year survival rate was 63% (95% CI: 51-76%).

Other published evidence

- 4.45. The Committee also reviewed evidence from a number of small retrospective observational studies, phase 1 dosing studies, case series, and literature reviews including regulatory approval summaries for the use of brentuximab vedotin in patients with relapsed refractory CD30 positive lymphomas:
- de Claro et al. Clin Cancer Res;18;5845-9;
 - Fanale et al. Clin Cancer Res. 2011;18;248-55;
 - Gibb et al. Haematologica. 2013;98;611-4;
 - Gravanis et al. Oncologist. 2016;21:102-9;
 - Salihoglu et al. Ann Hematol. 2015;94:415-20;
 - Shipp et al. N Engl J Med. 1993;329:987-94;
 - Theurich et al. J Clin Onc. 2013;31:59-63;
 - Younes et al. N Engl J Med. 2010;363:1812-21;
 - Zinzani PL et al. Crit Rev Oncol Hematol. 2016;104:65-70.

General Remarks

- 4.46. The Committee considered the evidence for the use of brentuximab vedotin for the treatment of CD30+ lymphomas was weak, generally of poor strength and quality, and lacking overall survival data. However, the Committee considered that the evidence for the treatment of relapsed refractory HL after auto-SCT to be relatively high quality as there is a phase III randomised controlled trial in this setting.
- 4.47. The Committee considered there was significant uncertainty regarding the most effective use of brentuximab vedotin treatment, as the funding and NPPA applications had requested end of line treatment but the evidence supported its preferential use in patients who were younger, with lower ECOG scores, and milder disease. The Committee considered that there was potential for brentuximab vedotin to be used earlier in the treatment algorithm.

- 4.48. The Committee noted that there appears to be a high level of response to treatment with brentuximab vedotin but there was uncertainty regarding the durability of response and level of benefit from this agent.
- 4.49. The Committee considered brentuximab vedotin was associated with a significant adverse event profile and there was a risk for harm if this agent were to be used in a broad range of indications.
- 4.50. The Committee considered there was currently a lack of evidence for the use of brentuximab vedotin in the treatment of CD30+ lymphomas including relapsed refractory HL or sALCL before to auto-SCT, for tandem auto/allo-SCT, or after-allo-SCT.
- 4.51. The Committee considered that based on currently available evidence brentuximab vedotin would provide the most benefit as a salvage treatment for potentially curative allo-SCT for those patients with relapsed refractory HL or sALCL who have had an auto-SCT and have not responded to standard salvage chemotherapy treatments.
- 4.52. The Committee noted that from the available evidence it appears only 5%-10% of patients treated with brentuximab vedotin following previous auto-SCT receive subsequent allo-SCT, and the outcome for these patients following allo-SCT is uncertain.
- 4.53. The Committee considered if brentuximab vedotin were funded it may result in an increase number of patients undergoing SCTs, but this was difficult to quantify.
- 4.54. The Committee noted there was no brentuximab vedotin product currently registered in New Zealand, but based on pricing detailed in NPPA applications the cost of this treatment appeared to be very high.

5. Recombinant Factor VIII and IX Fc Fusion Proteins for Haemophilia A and B

Application

- 5.1. The Committee considered funding applications from Biogen Idec NZ Pty Ltd for the new listing of their extended half-life (EHL) clotting factor replacement products efmoroctocog alfa (recombinant Factor VIII Fc fusion protein [rFVIII Fc]) and eftrenonacog alfa (recombinant Factor IX Fc fusion protein [rFIX Fc]) in the Pharmaceutical Schedule.

Recommendation

- 5.2. The Committee **recommended** that rFVIII Fc be listed in the Pharmaceutical Schedule, for the control and prevention of bleeding episodes in adults and children with congenital haemophilia A, only if cost-neutral to the currently listed preferred brand of short-acting rFVIII.
- 5.3. The Committee **recommended** that rFIX Fc be listed in the Pharmaceutical Schedule, for the control and prevention of bleeding episodes in adults and children with congenital haemophilia B, only if cost-neutral to the currently listed brands of short-acting rFIX.
- 5.4. The Committee **recommended** that PHARMAC seek further advice from the New Zealand Haemophilia Treaters Group (HTG) on the clinical inputs required to determine cost-neutrality to the short-acting clotting factor replacement products.
- 5.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 5.6. The Committee noted the currently registered indications for rFVIII Fc and rFIX Fc in New Zealand are for use in adults and children (≥ 12 years) with haemophilia A and B

respectively. rFVIII Fc and rFIX Fc are indicated for the control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes and perioperative management (surgical prophylaxis).

- 5.7. The Committee noted that an application to register rFVIII Fc for paediatric use (<12 years) has recently been submitted to Medsafe. The Committee also noted that a submission to register rFIX Fc for paediatric use (<12 years) has recently been submitted to the Australian Therapeutic Goods Administration (TGA), with submission to Medsafe planned following approval by the TGA.
- 5.8. The Committee noted that rFVIII Fc and rFIX Fc consist of a single molecule human coagulation factor covalently attached to the Fc domain of human immunoglobulin G1. The Fc portion enables binding to the neonatal Fc receptor, which is responsible for protecting immunoglobulin G from degradation and therefore prolonging the elimination half-life.
- 5.9. The Committee noted that prophylactic infusions with recombinant factor replacement products are the preferred treatment option, compared with episodic ('on-demand') treatment, due to the efficacy of prophylaxis in reducing the incidence of spontaneous or traumatic haemorrhages. A decreased number of haemorrhages, especially into the joints of the young, are associated long-term improvements in health outcomes. The Committee noted all people with severe haemophilia in New Zealand would be offered prophylaxis and that whilst there are different regimens for prophylaxis, the aim is to reduce bleed frequency by maintaining a trough factor $\geq 1\%$ of normal activity. The number of bleeds varies depending on individual patient factors and the presence of target joints and comorbidities.
- 5.10. The Committee noted factor replacement treatments are given by short intravenous infusion, and the primary benefit of EHL treatments is that they may require less frequent infusions to maintain a sufficient level of factor activity to prevent bleeding episodes.
- 5.11. The Committee noted that the health needs of people with haemophilia primarily relate to their increased risk of intra-articular and intramuscular haemorrhage that are associated with significant and debilitating pain, long-term joint damage and reduced mobility which may require joint replacement, difficulties with elective surgery including dental work, having to avoid or receive prophylactic treatment prior to sports or other activities, and possible restrictions on their type of employment. The Committee noted that whilst no material was presented on mortality, it seems likely that the majority of the current generation of people living with haemophilia are still likely to have a reduced life expectancy, even though many are now using the currently available prophylaxis treatments.
- 5.12. The Committee noted a prospective cohort study of 70 people with Haemophilia A and B living in the Auckland region of New Zealand (Young et al. Haemophilia. 2014;20:388-97) seeking to improve the number and speed of reports of episodes of bleeding. This study identified an approximate annualised bleed rate (ABR) of 4.3 in these participants which was extrapolated from the 5 month project period.
- 5.13. The Committee noted three papers (Santagostino et al. Haemophilia. 2014;20:527-34, Naraine et al. Haemophilia 2002;8:112-20, Wiedebusch et al. Haemophilia 2008;14:1014-22) investigating the health-related quality of life in people with haemophilia. Improvement in quality of life, as measured by 'HAEMO-QOL' and a standard gamble technique, show that patients receiving prophylaxis have an improved quality of life compared with those who use of on-demand treatment.
- 5.14. The Committee noted that carers for children are usually involved with the process of intravenous access required for treatment, and may have increased psychosocial strains and a reduced quality of life. The Committee noted the paper by Wiedebusch et al.

(Haemophilia. 2008;14:1014–22) cited concerns regarding the ‘future’ as being particularly associated with a poorer quality of life, however frequency of treatment wasn’t considered as a predictor of quality of life. In that study, parents of children with haemophilia experienced lower reductions in quality of life compared with parents of children with type 1 diabetes mellitus or juvenile arthritis.

rFVIII Fc

- 5.15. The Committee considered the clinical study report for ‘A-LONG’ (supplied as part of the applicant’s submission, published as Mahlangu et al. Blood. 2014;123:317-25), a Phase III open-label study in people 12 years or older with severe haemophilia A. Before study commencement, participants either had prior prophylactic twice weekly treatment or episodic treatment with more than 12 bleeds in the preceding year. The Committee noted limited randomisation occurred with all those on prior prophylaxis receiving individualized prophylaxis. Of those with prior episodic treatment, some chose to go to individualized prophylaxis, and those willing to be randomised were randomised to weekly prophylaxis or episodic treatment. Individualized prophylaxis was two initial doses and then between 25 and 65 IU/kg every 3 to 5 days to achieve FVIII between 1 and 3% or higher as needed to maintain good control of breakthrough bleeding. The weekly prophylaxis group received 65 IU/kg weekly, whilst the episodic treatment group received 10 to 50 IU/kg as required for the treatment of bleeding episodes.
- 5.16. The Committee noted the primary efficacy end points were ABR by electronic diary assessment and comparison of FVIII activity based on primary pharmacokinetic parameters. The mean dosing interval in the individualized prophylaxis group was 3.75 days with a last dose in the assessment period of 50.24 IU/kg per dose. The mean ABR in the individualized prophylaxis group was 2.91 with 64/117 (55%) having at least one bleed with 73.2 patient-years of follow up, calculated mean follow up per patient 0.63 years. In the weekly prophylaxis group the ABR was 8.81 with 19/23 (83%) had at least one bleed in 10.58 years of follow up, calculated mean follow up per patient 0.46 years.
- 5.17. The Committee noted that a 1.53-fold increase in the terminal factor VIII half-life for rFVIII Fc compared to standard rFVIII (19 hours versus 12.4 hours, $p < 0.001$), mean time to less than 1% factor activity was 4.9 days for rFVIII Fc compared to 3.3 days for standard rFVIII. The Committee noted this may on average equate to roughly twice weekly dosing for rFVIII Fc versus three times weekly for standard rFVIII. The Committee noted that some improvement in a haemophilia specific quality of life measure was evident in the clinical study reports; however The Committee considered that validity of that measure was not further substantiated and changes in quality of life were not reported in the published study.
- 5.18. The Subcommittee considered the clinical study report for ‘Kids A-LONG’ (supplied as part of the applicant’s submission, published as Young G et al. J Thromb Haemost. 2015;13:967-77), a phase III open-label study evaluating the safety, efficacy and pharmacokinetics of rFVIII Fc, in previously treated children with severe haemophilia A at a median age of five years. Most participants were already on prophylaxis with a median of two bleeds in the 12 months pre-study. Members noted subjects receiving a pre-study FVIII regimen of three intravenous infusions per week experienced an approximately 33% reduction in annual infusions with twice-weekly rFVIII Fc prophylaxis. The mean dosing interval was 3.46 days with a last dose in the assessment period of 46.2 IU/kg per dose. The mean on-study ABR was 2.62 with 37/67 (54%) having at least one bleed with 31.6 patient-years of follow up, calculated mean follow up per patient 0.47 years. This ABR was comparable with the rate observed in the 12 months pre-study for those on prophylaxis.
- 5.19. The Committee considered the clinical study report for ‘ASPIRE’ (supplied as part of the applicant’s submission, published as Nolan et al. Haemophilia. 2016;22:72-80), a Phase III open-label extension trial of A-LONG and Kids A-LONG. The mean dosing interval tailored prophylaxis group from A-LONG was 3.92 days with a mean weekly dose of

89.2 IU/kg and a calculated 50.0 IU/kg per dose. The Committee noted the mean ABR in the tailored prophylaxis group from A-LONG was 2.07 with 66/108 (61%) having at least one bleed in 148.3 patient-years of follow up, calculated mean follow up per patient 1.37 years.

- 5.20. The Committee noted the results of a cohort study of rFVIII (Recht et al. Haemophilia. 2009;15:869-80) may be a useful for a comparison of ABR's. Patients (n=94) who received a defined prophylaxis regimen of 30 (+/- 5) IU/kg three times weekly, with certain permitted dose increases if bleeding occurred, had a mean ABR of 3.9 with a mean half-life of 11 hours.

rFIXFc

- 5.21. The Committee considered the clinical study report for 'B-LONG' (supplied as part of the applicant's submission, published as Powell et al. N Engl J Med. 2013;369:2313-23), a Phase III open-label study in people 12 years or older with severe haemophilia B. Prior to commencement, participants either had prior prophylactic FIX treatment or episodic treatment with 8 or more bleeds in the last year.
- 5.22. The Committee noted participants were assigned by physician choice to weekly prophylaxis (initially 50 IU/kg weekly with dose adjusted to a target trough of 1% to 3% above baseline or higher, as clinically indicated), individualized prophylaxis (initially 100 IU/kg every 10 days with dosing interval adjusted to a target trough of 1% to 3% above baseline or higher, as clinically indicated) or episodic treatment 20 to 100 IU/kg. The study also included a perioperative group.
- 5.23. The Committee noted the primary efficacy end points were annualised bleed rate (ABR) by electronic diary assessment and comparison of FIX activity based on primary pharmacokinetic parameters. The mean dosing interval in the individualized prophylaxis group was 12.2 days and the mean dose in the fixed weekly prophylaxis group was 46.3 IU/kg. The mean ABR in the individualized prophylaxis group was 2.4 with 15/26 (58%) having at least one bleed in 28.5 patient-years of follow up, calculated mean follow up per patient 1.10. In the weekly prophylaxis group the ABR was 2.4 with 47/61 (75%) had at least one bleed in 53.6 patient-years of follow up, calculated mean follow up per patient 0.88. In the episodic treatment group the ABR was 18.4.
- 5.24. The Committee noted that a 2.4-fold increase in the terminal factor IX half-life for rFIXFc compared to standard rFIX (33.8 hours versus 82.1 hours, $p < 0.001$), mean time to less than 1% factor activity was 11.2 days for rFIXFc compared to 5.1 days for standard rFIX. The Committee noted this may allow the dosing interval to extend to once every one to two weeks for rFIXFc versus twice weekly for standard rFIX. The Committee noted that some improvement in a haemophilia specific quality of life measure was evident in the clinical study reports; however The Committee considered that validity of that measure was not further substantiated and changes in quality of life were not reported in the published study.
- 5.25. The Committee considered interim clinical study report for the extension study of B-LONG and Kids B-LONG (supplied in the applicant's submission). The ABR averaged over all the prophylaxis regimes was 3.6 (631 episodes over 173.59 patient years observation) and episodic was 16.7. The dosing was for the mean weekly dose 50 IU/kg was 50.3 IU/kg, while the for the fixed dose of 100 IU/kg the dosing interval was 12.3 days with a notable higher mean weekly dose of 58.1 IU/kg.
- 5.26. The Committee noted the results of a cohort study of rFIX (Kavakli et al. Haemophilia. 2016;22:381-8) may be a useful for a comparison of ABR's. The 25 patients who received once-weekly prophylaxis of 100 IU/kg for 52 weeks had a mean ABR of 3.6.

rFVIIIIFc and rFIXFc

- 5.27. The Committee considered it more likely that EHL products would be given at the same dose as the short-acting products with a reduced dose frequency, rather than a lower dose given at the same frequency. The total annual use of factor replacement in terms of IU may then be reduced with EHL products in proportion to the mean reduction in dose frequency possible. The Committee noted this may not be the same as the measured pharmacokinetic extension in half-life.
- 5.28. The Committee considered that the group most likely to benefit from EHL treatments are those with more difficult intravenous access and/or in children. Members noted that some children with haemophilia require implanted venous access devices; each time these are accessed there is a small risk of catheter related blood stream infection which may be reduced by EHL treatments.
- 5.29. The Committee also considered that a reduced infusion requirement may result in a health benefit to family and whanau, especially those with multiple family members with haemophilia or those who were less likely or less able to access treatment services at an optimal level, although the Committee noted there was no evidence was provided in the application to quantify any additional health benefit in these groups.
- 5.30. The Committee noted the fiscal risk associated with overall market growth if this made those people who are currently on on-demand treatment more amenable to receiving prophylaxis treatment with EHL.
- 5.31. The Committee considered the overall strength and quality of evidence for an effect for rFVIII Fc and rFIX Fc as moderate, however the strength of evidence for a differential effect compared to FVIII and FIX is poor, as this relies on indirect comparisons in open-label cohort studies. Overall the Committee considered that there is sufficient indirect evidence to suggest that rFIX Fc, and to a lesser extent rFVIII Fc, are likely to require fewer infusions, however no strong evidence was provided in the application for significantly reduced ABR's or improved quality of life for EHL products compared to current short-acting treatments.

6. Rituximab for myasthenia gravis

Application

- 6.1. The Committee considered an application from a clinician for the funding of rituximab for the treatment of myasthenia gravis (MG).

Recommendation

- 6.2. The Committee **recommended** that the funding of rituximab be widened to include patients with severe, rapidly progressive myasthenia gravis, as a third-line treatment, with a high priority.
- 6.3. The Committee **recommended** that the funding of rituximab be widened to include patients with myasthenia gravis that is considered for disease that follows the usual time course but is refractory to alternative treatments, as a third-line treatment, with a low priority, and that the recommendation for this patient group be reviewed by PTAC after the results of the randomised controlled trial comparing rituximab with placebo become available.
- 6.4. The Committee **recommended** that rituximab be used as a third- line treatment in these settings, following treatment with prednisone and one other immunosuppressant, and as such, be subject to Hospital Medicines List (HML) restrictions. The Committee requested that the Neurological Subcommittee provide advice regarding HML restrictions that use this proposed treatment algorithm.
- 6.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 6.6. The Committee noted that the applicant was requesting funding of rituximab for two patient groups; 1) patients with severe generalised or bulbar myasthenia gravis who are refractory i.e. requiring regular steroids or regular rescue treatment with IVIG or plasmapheresis, despite at least 12 months' consistent treatment with at least one immunosuppressive agent, 2) patients who have MG which is muscle-specific receptor tyrosine kinase antibody positive (MuSK Ab+) and a requirement for regular steroids (equivalent of 15 mg per day of prednisone for 6 months or longer) or two or more treatments with IVIG or plasmapheresis.
- 6.7. The Committee noted that the applicant considered the benefits of rituximab over other immunotherapies were a greater response rate (especially for those with MuSK Ab+ MG who may respond less well to other treatments), improved symptoms, fewer corticosteroid related side effects, reduced need for high dose corticosteroids, and reduced need for plasma exchange/intravenous immunoglobulin.
- 6.8. The Committee noted that PHARMAC had received four Named Patient Pharmaceutical Assessment applications for rituximab to treat refractory MG between July 2013 to July 2015. The Committee noted that rituximab is listed in the Pharmaceutical Schedule to treat numerous haematological, rheumatoid and autoimmune conditions, which include both registered and off-label indications.
- 6.9. The Committee noted that Medsafe has registered rituximab for the treatment of non-Hodgkin's lymphoma, Chronic lymphocytic leukaemia, rheumatoid arthritis, and Granulomatosis with polyangiitis (Wegener's) and Microscopic polyangitis. It noted that rituximab is not registered for the treatment of myasthenia gravis (MG).
- 6.10. The Committee noted that rituximab is a monoclonal antibody that is given via intravenous infusion and that infusion-related reactions may occur 30–120 minutes after starting the infusion and are most common with the first infusion.
- 6.11. The Committee noted that MG is a rare, progressive, autoimmune disease characterised by fluctuating skeletal muscle weakness associated with circulating muscle antibodies, either against the nicotinic acetylcholine receptor (anti-AChR; 80% of patients with generalised MG) or muscle-specific tyrosine kinase (anti-MUSK; 10%) of patients.
- 6.12. The Committee considered that patients with MG have a high health need. The Committee noted that overall mortality was significantly increased for subjects with AChR-antibody-seropositive myasthenia gravis compared with matched controls from the general population (mortality rate ratio 1.41, 95% CI 1.24-1.60) (Hansen et al. *Muscle Nerve* 2016;53:73). The Committee noted results from a large study of health related quality of life (HRQoL) in MG, which reported a mean physical composite score of 59 and mean mental composite score of 69 in people with MG, compared to the scores in matched healthy controls of approximately 77 and 80 respectively (Boldingh et al. *Health Qual Life Outcomes* 2015;13:115). The Committee noted that similar figures were reported by Twork et al. (*Health Qual Life Outcomes* 2010;8:129).
- 6.13. The Committee considered that the available evidence was of moderate strength (of effect) but weak quality, and considered that the results of the B Cell Targeted Treatment in Myasthenia Gravis – A Phase 2 Trial of Rituximab in Myasthenia Gravis (NN103 BeatMG randomised controlled trial. Nowak, unpublished) would provide more robust quality evidence. The results of this study which has closed recruitment should be available mid to late 2017. Members considered that the available studies for rituximab in MG consisted of case reports and small uncontrolled observational cohort studies, however they also considered that evidence for current treatments was not necessarily of high quality either.

6.14. The Committee noted a number of publications relating to the benefits of rituximab over other immunotherapies for the treatment of MG, including:

- *Iorio et al. J Neurol 2015;262:1115-9.* A systematic review and meta-analysis of the efficacy and safety of rituximab in myasthenia gravis. A total of 37 studies were identified and meta-analysis was performed on 15 studies. No randomised controlled trials were identified, so that in this report, only uncontrolled observational studies were included. Case reports and studies involving less than 2 patients in the AChR-IgG+, MuSK-IgG+ or seronegative groups were excluded from the metaanalysis. In total 168 patients were included, 91 patients were AChR-IgG+, 70 MuSK-IgG+ and 7 were double seronegative (dSN). The dose of rituximab was variable among studies. 137 patients received 4 cycles of 375 mg/m², 12 received 500 mg weekly, 8 were treated with 2 x 1 g while in other 11 patients different therapeutic regimens were adopted. The authors reported the overall response rate was 83.9% (event rate 0.839; 95% CI 0.765-0.893, p=0.000). The response rate was reported to be higher in the MuSK-IgG+ (88.8%) patients compared to AChR-IgG+ patients (80.4%) and double seronegative patients (85.6%). However the differences in the response rate among the different MG patient groups were reported as not statistically significant (no P values were provided). A meta-regression analysis did not report any significant correlation between the mean MG severity or the mean number of reinfusion and the response rate. An inverse correlation trend between disease duration and response rate to rituximab was reported, although it did not reach statistical significance (p=0.089). Adverse effects were reported in 7/168 patients (4.2%). Four patients had an infection (herpes zoster, giardiasis, bronchitis, pneumonia), two patients had prolonged B-cell depletion and one patient developed heart failure after the third rituximab infusion.
- *Nowak et al. Ther Adv Neurol Disord 2011;4:259-266.* A retrospective study of 14 refractory patients (6 AChR Ab+ and 8 MuSK Ab+) treated with rituximab. Patients were defined as refractory if their immunotherapy was unable to be lowered without clinical relapse, they were not clinically controlled on their immunotherapy or had severe side effects from the therapy. Rituximab was dosed at 375mg/m² weekly for 4 weeks repeated every 6 months. Objective MG scales were unable to be applied due to the retrospective design of the study. Clinical response was assessed qualitatively by comparing symptoms and exam findings before and after rituximab treatment. There were no predefined criteria used to state clinical response versus no clinical response. The authors reported a sustained clinical improvement was observed in all patients as well as a reduction of conventional immunotherapies. Prednisone dose was reported to decrease by a mean of 65.1%, 85.7% and 93.8% after cycle 1, 2 and 3 of rituximab therapy, respectively. A statistically significant reduction in plasma exchange sessions was observed after cycle 1 with all patients stopping plasma exchange after cycle 3. Acetylcholine receptor antibody titres decreased a mean of 40.2%, 52.1% and 67% post treatment cycle 1, 2 and 3 respectively (cycle 1: p=0.052; cycle 2: p=0.0046; cycle 3: data insufficient). Treatment was generally well tolerated. Six patients had infusion reactions, with three of these occurring during the first infusion. One patient developed leucopenia.
- *Lebrun et al. Eur J Neurol 2009;16:246-250.* An observational prospective study that followed 6 patients (2 MuSK Ab +, 1 AChR Ab +, and 2 seronegative) with refractory myasthenia. All patients had failed treatment with at least 2 standard treatments and had previously undergone thymectomy. Patients received 375mg/m² of rituximab weekly for 4 weeks, and then monthly for 2 months. After the initial phase, rituximab was given if patients reported worsening disease or the need to increase acetylcholinesterase inhibitors. Two patients needed repeat infusions for 1 year, and two patients for 2 years. Clinical improvement was noted in all patients within the first month of treatment, defined by investigators as their ability to perform clinical activities without weakness. All patients were eventually

tapered off acetylcholinesterase inhibitors, prednisone, and/or other immunosuppressant agents. Treatment with rituximab was well tolerated in all patients without significant adverse effects or opportunistic infections.

- *Collongues et al. Muscle Nerve 2008; 012;46:687-691.* Retrospective multicentre observational study that investigated the effect of rituximab in both refractory patients (n=13; 7 AChR Ab +, 3 MuSK Ab +, 1 both AChR Ab and MuSK Ab +, and 2 seronegative) and nonrefractory patients dependent on corticosteroids (n=7; 5 AChR Ab +, 1 MuSK Ab +, and 1 seronegative). Patients were deemed to be refractory if they failed to respond to thymectomy and at least 2 successive immunosuppressive drugs, with or without corticosteroids. All immunosuppressant agents were stopped before rituximab infusions except for corticosteroids. Rituximab was given via 2 different protocols: (1) 375mg/m² weekly for 4 weeks; and then 375mg/m² every 3 months or (2) 2x1g infusions given two weeks apart, then 1g as required if symptoms worsened. Patients were followed for 2 years. Relapses were treated with IVIG or plasmapheresis. In the refractory patients the annualised relapse rate decreased from 2.1 to 0.3 (p<0.001) compared with the 2 years before rituximab initiation. Myasthenia Gravis Foundation of America (MGFA) classification dropped from a range of 3b-5 to 0-4b. MGFA scores dropped from 5-3b to 4b-0 in refractory patients, and from 1.9 to 0.1 (P < 0.001) and 4b-2b to 3b-0 in non-refractory patients. No side effects were reported in either group, except for one case of spondylodiscitis 1 year after the last rituximab infusion. Within a year after rituximab induction, complete corticosteroid withdrawal was obtained in seven refractory and four non-refractory patients.
- *Diaz-Manera et al. Neurology 2012;78:189-193.* Clinical and immunologic long-term follow-up of 17 treatment refractory patients (6 MuSK Ab+ and 11 AChR Ab+) treated with rituximab. 'Treatment refractory' was defined as failure of at least 3 second line agents (eg. azathioprine, mycophenolate). Rituximab was given at a dose of 375mg/m² weekly for 4 weeks, then monthly for 2 months; re-infusions were given if symptoms worsened enough to interfere with activities of daily living. The mean duration of the follow-up was 31 months (range= 4 to 60). Ten of the AChR Ab+ patients were reported to have improved but six patients needed reinfusions. In contrast, all MuSK Ab+ patients achieved a remission (4/6) or minimal manifestations (2/6) status and no reinfusions were needed. Consequently, in the MuSK Ab+ group, prednisone doses were significantly reduced and concomitant immunosuppressant agents could be withdrawn. Clinical improvement was associated with a significant decrease in antibody titres in only six MuSK Ab+ patients. At the last follow-up MuSK antibodies were negative in three patients and showed a decrease of over 80% in the remaining three patients. Treatment was generally well tolerated except in two patients who had either facial flushing or generalised rash.
- *Illa et al. J Neuroimmunology 2008; 201:90-94.* A prospective observational study in six patients with severe refractory disease (3 AChR Ab+ and 3 MuSK Ab+). Patients received rituximab 375mg/m² weekly for 4 weeks, then monthly for 2 months. Patients were assessed according to the Myasthenia Gravis Foundation of America (MGFA) recommendations. Antibody titres to AChR and MuSK, Ig levels, and IgG subclasses, were tested before treatment and during a follow-up of 9-22 months. All patients (one class V and five class IVB), improved dramatically, with no side effects. Antibody titres declined in all patients (p=0.006). The decline was significantly better in MuSK+MG patients at 9 months (p=0.046) and correlated with a more sustained clinical improvement. Treatment was well tolerated with no adverse events being reported.

6.15. The Committee noted that the applicant has detailed that two different dosing regimens for rituximab may be used: 375mg/m² weekly for 4 weeks, and then every 3 months for 6 months; or 2 x 1g doses given 2 weeks apart, followed by an infusion of 1g as required if symptoms worsen. The Committee considered that that rituximab 375mg/m² weekly for

4 weeks was the most common dosing regimen used in studies. Members considered that some patients would have a response after a single 1g dose of rituximab, and that further doses may not be required for all patients.

- 6.16. The Committee noted that there are four therapies used to treat MG: symptomatic treatments (anticholinesterase agents), chronic immunomodulating treatments (high dose glucocorticoids and other immunosuppressant agents e.g. azathioprine, methotrexate, mycophenolate, ciclosporin, cyclophosphamide), rapid immunomodulating treatments (plasmapheresis and intravenous immunoglobulin) and surgical treatment (thymectomy). Members noted oral corticosteroid doses used in MG were often much higher and used for longer than those used in other autoimmune conditions, The Committee noted that when choosing the appropriate treatment, clinicians take into account the time and onset of the individual treatments, and the severity of the disease. The Committee noted the benefits and risks of these treatments, and members considered that current rapid immunomodulating treatments were expensive and immunosuppressant agents, such as ciclosporin and cyclophosphamide, had potential for serious adverse effects.
- 6.17. The Committee considered that patients who have MuSK Antibody positive disease may respond better to rituximab (Diaz-Manera et al., 2012; Iorio et al., 2015). The Committee noted that the Phase II RCT (in progress, unpublished, EudraCT 2015-005749-30) comparing rituximab with placebo has only recruited AChR antibody patients.
- 6.18. The Committee considered that the evidence of increased benefit for MuSK Antibody positive disease was of moderate strength but poor quality, and was not sufficient to recommend different or earlier treatment or to differentiate this group of patients from those with AChR antibody patients.
- 6.19. The Committee considered that patients are likely to require retreatment with rituximab for relapse of MG, and based on the available evidence, they considered that retreatment is likely to take place between 6 months and 2 years later.
- 6.20. The Committee noted that applicant estimated there would be 60 patients requiring treatment with rituximab for MG over 5 years, and considered this to be a reasonable estimate. The Committee considered approximately 10% of patients with MG would be refractory to existing funded treatments, which would be 18 to 81 prevalent patients in New Zealand. The Committee considered that these patients should have tried prednisone and at least one other immunosuppressant prior to rituximab. Members noted the number of patients that would require urgent treatment for severe rapidly progressive disease would be smaller.
- 6.21. The Committee considered that there was no evidence that MG disproportionately affected a population group that is already experiencing health disparity relative to the rest of the New Zealand population, and that there was no evidence reporting the severity of health needs of family and whanau of people with MG.
- 6.22. The Committee considered that the listing of rituximab may lead to savings related to corticosteroid side effects, and possibly would reduce specialist visits, hospital admissions and treatment with intravenous immunoglobulin and plasmapheresis, however it is difficult to determine the extent that these would be reduced.

7. Deflazacort for Duchenne muscular dystrophy

Application

- 7.1. The Committee considered a clinician's application for the funding of deflazacort for treatment of patients with Duchenne muscular dystrophy (DMD) who are unable to tolerate prednisone.

Recommendation

- 7.2. The Committee **recommended** that the application for the funding of deflazacort for the treatment of patients with DMD who are unable to tolerate prednisone be declined.
- 7.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 7.4. The Committee noted that DMD is the most common of all of the muscular dystrophies and primarily occurs in males at an incidence of approximately 1 in every 3500 male births, and is usually fatal by the 2nd or 3rd decade of life. The Committee noted that in addition to muscle weakness, common problems associated with DMD also include cardiac, pulmonary, orthopaedic, nutritional, growth, cognitive, and weight abnormalities.
- 7.5. The Committee noted that DMD symptoms usually appear in pre-school years, that children are usually wheelchair-bound by early adolescence, and die in their late teens or twenties from respiratory insufficiency or cardiomyopathy (Passamano et al. *Acta Myol.* 2012;31:121-5). The Committee considered that patients with DMD have a very high health need.
- 7.6. The Committee noted the findings of Cavazza et al. (*Eur J Health Econ* 2016;17:19-29) which reported that there was a self-reported HR-QoL of 0.24 for DMD (a disutility of 0.76) and a self-reported HR-QoL of 0.71 for caregivers of people with DMD (a disutility of 0.29). The Committee noted that Cavazza et al. (2016) also reported that informal care (unpaid care usually provided by family members) is the major cost associated with the care of those with DMD. The Committee considered that the health need of families, whanau and wider society was significant given that, in addition to this decreased quality of life, there was an increased risk of depressive episodes, increased parent-child dysfunction and decreased psychological adjustment.
- 7.7. The Committee noted that the first-line treatment for DMD was prednisone which was typically started at around 5 years of age, and that patients remain on prednisone at 0.75mg/kg/day until adverse effects outweigh any clinical gain or upper limb function is clinically poor. The Committee noted that prednisone may cause weight gain and behavioural side effects.
- 7.8. The Committee considered that DMD did not disproportionately affect a population group that is already experiencing health disparity relative to the rest of the New Zealand population.
- 7.9. The Committee noted that the applicant was requesting funding of deflazacort for patients with DMD who are unable to tolerate prednisone. The Committee noted the applicant's view, which references Gloss et al. (*Neurology* 2016;86:465-72), that the benefits of deflazacort over prednisone are reduced weight gain, delayed loss of ambulation and survival gain, and anecdotally, improved behavioural side effects. The Committee noted some families were self-funding deflazacort, which might be evidence of an unmet health need in patients who cannot tolerate prednisone.
- 7.10. The Committee noted that deflazacort is an unregistered medication and that three Named Patient Pharmaceutical Assessment applications for deflazacort for DMD had been received by PHARMAC since March 2012 when the Named Patient Pharmaceutical Assessment policy came into effect.
- 7.11. The Committee considered that as prednisone and deflazacort were both glucocorticosteroids, with very similar structures, their pharmacological mode of action was the same. The Committee considered that deflazacort 0.9 mg/kg/day is clinically equivalent to prednisone 0.75 mg/kg/day, and at this dose both deflazacort and prednisone would be expected to have similar therapeutic effects and side effects.

- 7.12. The Committee considered that if a recommendation was made to list deflazacort on the Pharmaceutical Schedule, that the patient population that would most benefit from deflazacort would be patients with DMD that have trialed, and had adverse effects from, treatment with prednisone. The Committee considered that if deflazacort was funded, it would replace prednisone and would be used in combination with medications to support bone, respiratory and cardiovascular complications of DMD (as is also the case for prednisone). The Committee noted Gloss et al (Neurology 2016;86;465-72) reported that there may be a greater risk of cataracts when using deflazacort over prednisone. The Committee considered that, if deflazacort was funded, likely consequences to the health system may include an increase in ophthalmology consultations due to an increase in the incidence of cataracts (Gloss et al. Neurology 2016;86;465-72), and subsequently an increase in patients undergoing cataract surgery. The Committee considered that deflazacort is likely to result in people being treated for longer than they are currently treated with prednisone, but the Committee was unable to quantify what the length of treatment would be. The Committee considered PHARMAC's estimate of patient numbers to be a realistic approximation of the number of DMD patients that would be treated with deflazacort.
- 7.13. The Committee noted and reviewed Bello et al. (Neurology 2015;85:1048-55), an observational study of age at loss of ambulation (LoA) and side effect profiles associated with prednisone and deflazacort regimens in 340 participants with DMD. In a Cox regression analysis adjusted for dose and regimen, deflazacort was reported to be associated with a lower yearly risk of LoA than prednisone or prednisolone (HR 0.294 ± 0.053 versus 0.490 ± 0.08, p=0.003). In participants who were treated with a daily regimen, a later median LoA was observed with deflazacort compared with prednisone or prednisolone (13.9 years versus 11.2 years). Deflazacort was reported to show higher frequencies of growth delay (p<0.001), cushingoid appearance (p=0.002), and cataracts (p<0.001), but not of weight gain. The Committee considered that the study by Bello et al. (2015) was weak non experimental evidence that deflazacort may have greater delay to loss of ambulation than prednisone, but that the results are subject to considerable confounding. The Committee noted that the small randomised controlled trials in the available evidence did not indicate that deflazacort may provide a greater delay to loss of ambulation than prednisone.
- 7.14. The Committee noted Biggar et al. 2006 (Neuromuscul Disord. 2006;16:249-55), a retrospective cohort study of 74 patients comparing deflazacort with non-randomised controls, and Schram et al. (J Am Coll Cardiol 2013;61:948-54) a retrospective cohort review comparing 86 patients on prednisone, deflazacort or mixed treatment with non-randomised controls. The Committee noted that a survival gain was reported in these trials, but considered that the available evidence was of low quality.
- 7.15. The Committee noted Matthews et al. (Cochrane Database Syst Rev. 2016;5:CD003725), a systematic review of the use of corticosteroids in DMD. The review included randomised controlled trials (RCTs) or quasi-RCTs of corticosteroids (eg prednisone, prednisolone, and deflazacort) given for a minimum of three months to patients with a definite DMD diagnosis. Twelve studies involving 667 participants and two new ongoing studies were identified for inclusion. The Committee noted that the authors reported that after 12 months of treatment that patient mean weight was 9.52% (4.12-14.91%) higher in those treated with prednisone than in those treated with deflazacort. The Committee considered that this meta-analysis of RCTs was derived from a small number of participants and that the two trials that most of this result was derived from had a considerable risk of bias.
- 7.16. The Committee noted that in the observational study of Bello et al. (Neurology 2015;85:1048-55) the side effect profiles associated with prednisone and deflazacort regimens in DMD were reported for 14 different treatment regimens. The authors reported similar proportions of weight gain for those that stayed on the corticosteroid that they were initially commenced on. In those who switched from prednisone to deflazacort more patients had concerns regarding increased weight compared to those

who remained on their original corticosteroid. However weight gain over time was not reported by corticosteroid. The Committee noted Balaban et al. (Am J Phys Med Rehabil 2005;84:843-50), a retrospective study of 49 boys comparing the beneficial and adverse effects of deflazacort with prednisone, and noted that the results reported a decrease in the weight difference between those treated with deflazacort and prednisone over time. The Committee considered that both these trials may be at risk of publication bias and selection bias.

- 7.17. The Committee noted and reviewed the evidence from RCT and non-randomised cohorts provided by the applicant, and considered that there was no difference in the absolute number of patients with behavioural side effects in patients who were treated with deflazacort when compared with those who were treated with prednisone. The Committee considered that there was no evidence at this time to suggest that the use of deflazacort would result in a reduction in the use of pharmaceutical treatments to treat behavioural issues, and considered that behavioural issues in patients with DMD would generally be managed with non-pharmaceutical treatments.
- 7.18. The Committee noted that there was little published evidence relating to a health benefit for family, whanau or wider society, in addition to the health benefits for people with DMD. The Committee considered that preserving ambulation and preserving feeding in those with DMD may improve the quality of life of caregivers.
- 7.19. The Committee noted the prices for the liquid and tablet formulations of deflazacort that were given by the applicant and PHARMAC staff, noting the high price and the large price difference between the tablet and liquid formulations. The Committee considered that the oral liquid would offer little health gain over the tablets and this would not justify the higher price for the oral liquid. The Committee considered that crushing the deflazacort tablets may be a suitable alternative to the liquid formulation.
- 7.20. The Committee considered that the evidence for pharmaceutical treatment with glucocorticoids to prevent decline of DMD was of high strength and high quality. The Committee considered that the available evidence in support of deflazacort as an alternative to prednisone was low quality and did not support a benefit of deflazacort over prednisone in the requested patient population.
- 7.21. The Committee noted that there was an ongoing randomised controlled trial (the FOR-DMD study) comparing prednisone with deflazacort in boys with confirmed DMD, with planned follow-up of between 3 to 6 years. The Committee requested that this trial be brought to the Committee for review once it was published.

8. Azithromycin – for treatment of bronchiolitis obliterans syndrome (BOS) in patients who have received stem cell/bone marrow transplant

Application

- 8.1. The Committee considered a clinician funding application from a paediatric haematologist for the widening of access to azithromycin for the treatment of bronchiolitis obliterans syndrome (BOS) in patients who have received stem cell transplant (SCT/BMT).

Recommendation

- 8.2. The Committee **recommended** access to azithromycin be widened to include the treatment of BOS post SCT/BMT with a high priority in both the community and in hospital.
- 8.3. The Committee **recommended** the prescriber for this indication be any relevant specialist prescribing for a patient with a confirmed diagnosis of BOS, and that the treatment be in line with the treatment of BOS following lung transplant. The Committee

recommended that azithromycin for this indication be available under the following criteria:

Initial application - (bronchiolitis obliterans syndrome, in patients post stem cell transplant/bone marrow transplant) from any relevant specialist. Approvals valid without further renewal unless notified where the patient has received a stem cell transplant or bone marrow transplant and has a confirmed diagnosis of bronchiolitis obliterans syndrome and requires treatment for bronchiolitis obliterans syndrome*.

Indications marked with * are Unapproved Indications

- 8.4. The Committee considered the mechanism for this restriction, for example subsidy by endorsement or special authority, it considered that this should be in line with the restriction for BOS following lung transplant.
- 8.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Discussion

- 8.6. The Committee noted that azithromycin is currently available for the treatment and prophylaxis of BOS in patients who have received a lung transplant. Members noted the applicant considered the pathology of BOS to be similar in SCT/BMT and lung transplant recipients. The Committee noted PHARMAC had received a small number of Named Patient Pharmaceutical Assessment (NPPA) applications for use of azithromycin for the treatment of BOS post SCT/BMT. Members considered that these patients have a high health need.
- 8.7. The Committee considered the new patient numbers who would be treated for BOS following SCT/BMT would be small (estimated to be less than 10 patients per annum). Members noted the low cost of azithromycin tablets and minimal fiscal risk of funding treatment for this high health need group.
- 8.8. The Committee noted there is some evidence available regarding the use of azithromycin in treatment of BOS post SCT/BMT. The Committee noted two small trials that it considered provided conflicting evidence on the use of azithromycin for BOS between two types of transplants, lung transplants and bone marrow/stem cell transplant. Lam et al. (Bone Marrow Transplant. 2011;46:1551-6) reported no significant benefit of 3 months of oral azithromycin on the respiratory symptoms and lung function in 22 patients with relatively late BOS following SCT. However, the Committee noted that Corris et al. (Thorax. 2015;70:442-50) reported significant improvements in FEV1 with azithromycin compared with placebo ($p=0.02$) for the treatment of BOS in lung transplantation. The Committee noted that the Lam et al. trial authors had surmised that the mechanisms underlying BOS in SCT could be different from those in BOS following lung transplantation and had suggested further studies in the early phases of BOS following SCT take place.
- 8.9. The Committee noted a small prospective observational study (Kahlid et al. Eur Respir J, 2005;25:490-3) of the use of azithromycin in 8 patients who developed BOS post BMT. Seven of the 8 demonstrated significant improvement in lung function after azithromycin treatment for 12 weeks (250mg three times a week). The mean change in FVC after treatment was 410 mL (95% CI, 0.16–0.65; $p < 0.0052$), representing an average increase in FEV1 of 21%. Patients with improved pulmonary function tests also showed significant improvement in shortness of breath and exercise tolerance.
- 8.10. The Committee considered evidence to support azithromycin prophylaxis in this patient group to be extremely limited and that any recommendation on prophylaxis post SCT/BMT should be deferred until the results of the French 'ALLOZITHRO' randomised controlled trial (ClinicalTrials.gov NCT01959100) are available.
- 8.11. The Committee considered azithromycin use in patients post SCT/BMT with confirmed BOS should be limited to treatment only. It also considered that other access restrictions

should be consistent with those in place for patients following lung transplant who develop BOS.

Azithromycin discussion following May 2016 consultation feedback

- 8.12. The Committee noted that in May 2016 PHARMAC released a consultation document seeking feedback on a proposal to fund azithromycin for non-cystic fibrosis (non-CF) bronchiectasis in children and make other amendments to the access of azithromycin. Notably these amendments included the withdrawal of the ability to access up to 5 days of azithromycin treatment for any indication. The Committee noted that PHARMAC received feedback, raising potential clinical issues which PHARMAC staff now sought PTAC advice on.

Widening access for patients with non-CF bronchiectasis

Recommendation

- 8.13. The Committee **recommended** that prescribers of azithromycin for non-CF bronchiectasis be limited to Respiratory Physicians and to Paediatricians, and there be a 12 month stand-down period between azithromycin treatments, unless deemed clinically inappropriate to stand-down, with no more than 24 months cumulative treatment from all courses combined.
- 8.14. The Committee recommended the following Special Authority (amendments to proposed criteria from consultation as follows – additions in bold, deletions in strikethrough):

Initial application – (non-cystic fibrosis bronchiectasis*) ~~from any relevant practitioner~~ **Only from a respiratory physician or a paediatrician**. Approvals valid for 12 months for applications meeting the following criteria:

- 1) For prophylaxis of exacerbations of non-cystic fibrosis bronchiectasis*; and
- 2) Patient is aged 18 and under; and
- 3) Either:
 - 3.1. Patient has had 3 or more exacerbations of their bronchiectasis, within a 12 month period; or
 - 3.2. Patient has had 3 acute admissions to hospital for treatment of infective respiratory exacerbations within a 12 month period.

Indications marked with * are Unapproved Indications

Renewal application – (non-cystic fibrosis bronchiectasis*) ~~from any relevant practitioner~~ **Only from a respiratory physician or a paediatrician**. Approvals valid for 12 months for applications meeting the following criteria:

- 1) **The patient has completed 12 months of azithromycin treatment for non-cystic fibrosis bronchiectasis; and**
- 2) **Following initial 12 months of treatment, the patient has not received any further azithromycin treatment for non-cystic fibrosis bronchiectasis for a further 12 months, unless considered clinically inappropriate to stop treatment; and**
- 3) **The patient will not receive more than a total of 24 months azithromycin cumulative treatment (see note)**
- 4) ~~The treatment remains appropriate and the patient is benefitting from treatment; and~~
- 5) ~~The patient will not be prescribed more than a further 12 months' treatment (see note).~~

Note: no further renewals will be subsidised. A maximum of 24 months of azithromycin treatment for non-cystic fibrosis will be subsidised.

Indications marked with * are Unapproved Indications

Discussion

- 8.15. The Committee noted the feedback received in response to PHARMAC's May 2016 consultation document on amendments to the listing of azithromycin raised concerns regarding antimicrobial stewardship.
- 8.16. The Committee considered that there was no need to re-evaluate the evidence for treatment with azithromycin for this indication, as this had been considered previously.
- 8.17. The Committee noted the two main issues raised in consultation that were relevant to this discussion were, firstly, whether a 12 month gap should be mandatory as a stand-down between the two proposed courses of azithromycin for non-CF bronchiectasis and, secondly, whether 'any relevant prescriber' is an appropriate restriction.

- 8.18. The Committee noted its role in antimicrobial stewardship (AMS) within PHARMAC, and in turn PHARMAC's role within wider efforts by the health sector to improve AMS, particularly the national antimicrobial resistance (AMR) framework work led jointly by the Ministry of Health and the Ministry for Primary Industries. The Committee considered that it is not currently its role to determine which specific medications should be used in preference to others as a result of AMS, particularly given inter-regional variation in microbial sensitivity and antimicrobial protocols, rendering specific funding restrictions problematic when on a PHARMAC-funding national scale.
- 8.19. The Committee considered a 12 month stand-down period between the initial 12 months of treatment and the subsequent 12 months of treatment should be incorporated into the renewal criteria, unless considered clinically inappropriate. Members also considered the criteria should be more explicit regarding total period of prophylaxis (no more than 24 months cumulatively). The Committee remained in support of funding azithromycin for this indication with the amended prescriber criteria and stand-down period being included in the criteria.
- 8.20. Members noted a retrospective follow-up by Samson et al. (Resp Medicine 2016:117:1-6) observing long-term effects of azithromycin in patients with cystic fibrosis, which reported no clinical benefit of low-dose azithromycin were present after one year of treatment in young CF patients, where selection for macrolide resistant strains of bacteria occurred, which the authors considered should lead to a reconsideration of the duration of azithromycin treatment in CF. The Committee recommended this paper be reviewed by the Anti-infective Subcommittee at its next meeting.

Removing the funding for a maximum of 5 days' treatment for any indication

Recommendation

- 8.21. The Committee recommended that the proposal to restrict 5 day courses of azithromycin not be progressed.
- 8.22. The Committee recommended that the proposed funding criteria for Special Authority should still be progressed for longer term treatment indications and the *Mycobacterium avium intracellulare* complex infection indication be expanded to include all mycobacterium infections.
- 8.23. The Committee recommended the following Special Authority (amendments to proposed criteria from consultation as follows – additions in bold, deletions in strikethrough):
- Initial application - (bronchiolitis obliterans syndrome, cystic fibrosis and *Mycobacterium avium intracellulare* ~~complex~~ infections) from any relevant ~~practitioner~~ **specialist**. Approvals valid without further renewal unless notified where the patient has any of the following:
- 1) Cystic fibrosis and has chronic infection with *Pseudomonas aeruginosa* or *Pseudomonas* related gram negative organisms*; or
 - 2) *Mycobacterium avium intracellulare* ~~complex~~ infections.
 - 3) Received a lung transplant and requires treatment or prophylaxis for bronchiolitis obliterans syndrome*; or
 - 4) Received stem cell transplant and requires treatment for bronchiolitis obliterans syndrome* and has a confirmed diagnosis.
- Indications marked with * are Unapproved Indications
- 8.24. The Committee considered that these criteria could be applied via endorsement if appropriate.
- 8.25. The Committee **recommended** that the Anti-infective Subcommittee further discuss the use of azithromycin for 5 days treatment at its next meeting.
- 8.26. The Committee **suggested** that PHARMAC write to the Ministry of Health regarding Antimicrobial Stewardship.

Discussion

- 8.27. The Committee noted that azithromycin is currently available on the Pharmaceutical Schedule and may be prescribed for up to 5 days of treatment without restriction. The Committee noted feedback received in response to PHARMAC's May 2016 consultation document regarding a proposal to limit such 5 day courses of azithromycin in the community to specific indications (being *Mycoplasma genitalium* infection when first-line treatments have failed, pertussis and chlamydia).
- 8.28. The Committee further noted the majority of feedback was with respect to Community Acquired Pneumonia (CAP), but also included feedback on other indications such as typhoid fever and some other minor indications.
- 8.29. The Committee noted that across the DHBs there are differing clinical treatment guidelines, where some DHBs recommend using azithromycin for mild through to extremely severe CAP, however other DHBs do not recommend azithromycin in their recommendations for CAP.
- 8.30. The Committee noted a BPAC article (www.bpac.org.nz/BPJ/2014/April/upfront.aspx) on azithromycin reporting the USA experiencing 30% *Streptococcus pneumoniae* resistance to macrolides occurring concurrently with azithromycin becoming the most prescribed antibiotic in the USA. Subsequently these rates had fallen in association with introducing conjugate pneumococcal vaccines.
- 8.31. The Committee noted caution with azithromycin usage and the development of resistance, potentially due to its very long half-life; however the Committee noted that the exact mechanism of the development of resistance is not well understood.
- 8.32. The Committee noted its role in antimicrobial stewardship (AMS) within PHARMAC, and in turn PHARMAC's role within wider efforts by the health sector to improve AMS. The Committee also reiterated that it considered its current role does not include determining which specific medications should be used in preference to others as a result of AMS, particularly given inter-regional variation in microbial sensitivity and antimicrobial protocols.
- 8.33. The Committee noted again the antimicrobial stewardship work currently being co-led by the Ministry of Health and the Ministry for Primary Industries which PHARMAC staff are participating in. The Committee considered that valuable feedback in the form of consultation responses were being provided by DHB antimicrobial stewardship committees. PTAC considered that these DHB antimicrobial stewardship committees should be able to use a national funding framework and apply their own regional variations. The Committee considered that the consultation had highlighted an important need for PHARMAC to continue its engagement with the Ministry of Health and other organisations to foster AMS leadership.

9. Nintedanib for idiopathic pulmonary fibrosis

Application

- 9.1. The Committee considered a submission from Boehringer Ingelheim for the funding of nintedanib (Ofev) for the treatment of idiopathic pulmonary fibrosis.

Recommendation

- 9.2. The Committee noted that another treatment for idiopathic pulmonary fibrosis, pirfenidone, had recently received a high recommendation for listing from the Respiratory Subcommittee and **recommended** that, if pirfenidone were to be listed, nintedanib be funded cost-neutral to pirfenidone.

- 9.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 9.4. The Committee noted that idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible and usually lethal disease of unknown cause, being a form of chronic fibrosing interstitial pneumonia limited to the lung and occurring mainly in older patients. The Committee also noted that in the United States, IPF affects between 150– 200,000 people per year with as many as 40,000 deaths and that extrapolating these numbers to New Zealand may mean as many as 2,100 to 2,800 cases with 500 to 600 deaths per year.
- 9.5. The Committee noted retrospective analysis of an IPF database managed by Auckland District Health Board (ADHB) over the period January 1986 and May 2001 (Young et al. *Respirology*. 2006;11:467-70. The study identified 87 cases of IPF, with ethnicity data available for 84 cases, and reported IPF having a lower incidence in Māori and Pacific peoples with 2% (2/84) Māori and 0% Pacific peoples prevalence (the authors noted that this was only a preliminary observation, and that it warrants further investigation).
- 9.6. The Committee noted that making a definitive diagnosis of IPF is difficult as all other causes of interstitial lung disease would need to be eliminated first. The Committee noted that the main symptoms of IPF are chronic dyspnoea and an unproductive cough. Members also noted that the diagnostic criteria included the presence of honeycombing seen on high resolution computed tomography (HRCT) and specific histopathologic changes on lung biopsy.
- 9.7. The Committee noted the prognosis in IPF is poor. Some retrospective studies report median overall survival times from diagnosis of 2 to 3 years, but other studies report 25% of patients survive 5 years (which may be due to earlier diagnosis, or a subset of patients with less progressive disease). Some patients experience rapid decline while others progress more slowly, with others having periods of relative stability interspersed with acute deteriorations in respiratory function. The Committee noted co-morbidities include pulmonary arterial hypertension (PAH), cardiovascular disease and emphysema, all of which worsen prognosis, and approximately three quarters of patients have gastrointestinal reflux disease (GORD).
- 9.8. The Committee noted the pulmonary tests most commonly associated with prognosis of IPF are forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity of the lungs for carbon monoxide (DLco), and also noted that the clinical trials supporting the registration of nintedanib had reported the decline of FVC as a measurement of improvement.
- 9.9. The Committee noted a retrospective review of 446 patients with IPF patients categorised as having mild, moderate or severe disease by FVC% (>70%, 55-69%, and 55% respectively) reported median survival times of 55.6, 38.7 and 27.4 months respectively, while those categorised by DLco (>50%, 35-49% and <35%) had respective median survival times of 67.3, 47.8 and 31.3 months (Nathan. *Chest* 2011;140:221-9). The Committee noted that, internationally, there has been considerable discussion around the validity of FVC, and decline in FVC over a fixed period of time, as a measure of clinical response; there are some clinical scenarios where patients may have very significant IPF but maintain an FVC of over 70- 80%. Members however considered that currently, FVC is a valid measure of disease state, with the minimal clinically important difference (MCID) being between 2% and 6% reduction in FVC (Du Bois et al. *Am J Respir Crit Care Med*. 2011;184:1382-9).
- 9.10. The Committee noted that in IPF, a decline in FVC over a 6 or 12 month period of >10% is predictive of mortality and marginal declines of 5 to 10% are associated with a decrease in survival (Du Bois et al. *Am J Respir Crit Care Med*. 2011;184:1382-9). The Committee noted that in two clinical trials the one year mortality rate was five-fold higher

in patients with absolute declines in FVC% predicted of over 10% over a 24 week period (HR 4.78; 95% CI 3.12-7.33) and two-fold higher in those with absolute declines of 5 to 10% (HR 2.14; 95% CI 1.43-3.20) compared with patients with declines of less than 5% (Du Bois et al. 2011). Other predictors of mortality are a decline in the 6-minute walk test distance of >50 meters, a reduction in the alveolar-arterial oxygen tension gradient of >15mmHg at 12 months and the extent of fibrosis and honeycombing on High Resolution CT (HRCT).

- 9.11. The Committee noted that, a number of treatments have been used for IPF including interferon gamma-1 β , bosentan, ambrisentan, anticoagulants, corticosteroids and immunosuppressants e.g. azathioprine, cyclophosphamide: based on the hypothesis that IPF is an inflammatory disorder, but that these are not considered effective treatment options, and there are currently no other efficacious treatments except pirfenidone or lung transplantation. The most important components of supportive care for patients with IPF are stopping smoking, the provision of supplemental oxygen (when needed), education, pulmonary rehabilitation, and vaccination against *Streptococcus pneumoniae* and influenza. The Committee noted that IPF is the most common interstitial lung disease among referrals for lung transplantation and the second most frequent disease for which lung transplantation is performed.
- 9.12. The Committee noted the commentary that there is a high prevalence of GORD in patients with IPF, including asymptomatic reflux to proximal oesophagus (Wells et al. Curr Opin Pulm Med 2014;20:442–8 Appendix 5). A recent meta-analysis of the placebo arms of three U.S “IPF-net” studies reported that patients receiving antacids were ‘characterised’ with a significantly slower decline in FVC (Lee et al. Lancet Respir Med. 2013;5:369–76 Appendix 5). Wells et al. 2014 also considered that while further RCTs were needed to establish a direct association between managing reflux and slowed disease progression, it was reasonable to recommend treatment of reflux in symptomatic patients.
- 9.13. The Committee noted that there were three main clinical trials of nintedanib; it considered the quality of evidence of these three trials was good, but the strength, assessed by the effect size, was low:
- 9.14. TOMORROW (Richeldi et al N Engl J Med. 2011;365:1079-87) was a 12 month, randomised double-blind placebo controlled, phase 2 trial evaluating the efficacy and safety of four different oral doses of nintedanib. A total of 432 patients were randomly assigned to one of four oral doses of nintedanib or placebo. The baseline median FVC in litres was similar across all groups, ranging from 2.7 L to 2.8 L. Results on primary endpoint of annual rate of change in FVC reported the group taking the highest dose, 150 mg twice daily, showed a trend towards a slower decline in lung function of 0.06 litres per year compared with 0.19 litres per year in placebo group. The pre-specified secondary outcome results were:
- Decrease in FVC of more than 10% or more than 200 ml: smaller in the highest-dose group than in placebo, 23.8% versus 44% (p=0.004), respectively.
 - DL_{CO} or distance achieved in the 6 minute walk test: no significant differences between any of the groups receiving nintedanib and the placebo group.
 - SGRQ (St George’s Respiratory Questionnaire score): a small reduction for the 150 mg BD group compared with an increase for the placebo group, adjusted mean absolute change from baseline -0.66 points versus 5.46 points respectively (p=0.007).
 - Incidence of acute exacerbations: fewer for the 150 mg BD dosing compared with placebo, 2.4 versus 15.7 per 100 patient-years (p=0.02) respectively.
 - Deaths from any cause: no significant differences between any of the groups, with 11, 3, 4 and 7 all-cause deaths in the active treatment groups and 9 deaths in the placebo group.

- 9.15. INPULSIS-1 (515 patients) and INPULSIS-2 (555 patients) trials (Richeldi L et al. *N Engl J Med.* 2014;370:2071-82) were simultaneous randomised, double-blind, phase 3 trials evaluating the efficacy and safety of 150 mg BD of nintedanib over placebo in patients with IPF over 52-week. The Committee noted that eligible patients were aged over 40 years with a diagnosis of IPF within 5 years of randomisation who had undergone a chest HRCT scan within a year prior to screening, had an FVC predicted of >50%, forced expiratory volume in 1 second (FEV₁/FVC) of 0.7 and a diffusing capacity for carbon monoxide (DLco) of 30-70% predicted. The primary endpoint for each trial was the annual rate of decline in FVC, with key secondary endpoints being changes from baseline in the total score on the St George's Respiratory Questionnaire (SGRQ) over 52 weeks and times to first exacerbation. Concomitant therapy with up to 15mg/day of prednisone was permitted (21% of patients) but patients on high dose prednisone, acetylcysteine or azathioprine were excluded.
- 9.16. The Committee noted that in INPULSIS-1 there was a difference of 125.3 mL/year (P<0.001) in FVC, with INPULSIS-2 differing by 93.7 mL/year, indicating overall a 50% relative reduction in lung function decline over 52 weeks. In both trials, nintedanib recipients were significantly (p=0.001) more likely to be stable at 52 weeks than placebo recipients, whilst in the INPULSIS-1 trial alone there was no absolute decline in percent predicted FVC of >10% (70.6 versus 56.9%) – the latter was not found in INPULSIS -2 (69.6 versus 63.9%).
- 9.17. The Committee noted that the risk of progression (absolute decline in percent predicted FVC of <10% or death) was significantly reduced in the nintedanib versus placebo arms by 47% in INPULSIS-1 (24.3 versus 40.7%), [hazard ratio [HR] 0.53; 95% CI 0.39-1.72; p=0.0001], 33% in INPULSIS-2 (29.8 versus 42.0%) [HR 0.67, 95% CI 0.51-0.89; p=0.0054] and 40% in the pooled analysis (27.1 versus 41.4%) [HR 0.60; 95%CI 0.49-0.74; p<0.0001].
- 9.18. The Committee noted that secondary end-points were improved in INPULSIS-1 but not in INPULSIS-2, but in a pre-specified pooled analysis there was a significant extension of the time to the first acute exacerbation as judged by a central adjudicated panel. Adjudicated acute exacerbation events occurred in 1.9% of nintedanib recipient and 5.6% of placebo recipients. Members noted a lack of data to suggest nintedanib treatment resulted in significantly improved quality of life, as evidenced by the lack of statistical difference in the adjusted mean change from baseline to week 52 in the SGRQ score between the treatment and placebo arms. The Committee noted that while there was a trend to overall survival with nintedanib, this did not reach statistical significance, but noted the study was not powered for mortality.
- 9.19. The Committee noted that in pooled analysis the effect of nintedanib on the annual rate of decline in FVC appears to be consistent across various pre-specified groups including sex, age, race, baseline FVC percentage predicted, baselines SGRQ, smoking status, systemic corticosteroid use and bronchodilator use.
- 9.20. The Committee noted the results of an extension study of INPULSIS-1 and 2 (INPULSIS-ON) suggest that the effect on slowing disease progression is maintained beyond 52 weeks and that patients with severely impaired FVC may still receive the same benefit from nintedanib in reducing the rate of decline in FVC as patients with less impairment (Wuyts. *Lung.* 2016 Jul 4. [Epub ahead of print]).
- 9.21. The Committee noted the most commonly reported adverse event with treatment in all trials was diarrhoea (60%), mostly mild or moderate in intensity leading to discontinuation in less than 5% of patients. Elevated liver enzymes were more common in patients treated with nintedanib (4.9 – 5.2%) than placebo (0.5 – 0.9%) and more patients on nintedanib had a myocardial infarction (1.5 – 1.6% versus 0.5%).
- 9.22. The Committee noted a network meta-analysis of new treatments for IPF (Loveman et al. *BMC Pulm Med.*2015;15:37) included 11 studies, and of the treatments reviewed,

only pirfenidone and nintedanib produced statistically significant results in slowing in the rate of FVC compared with placebo (pirfenidone odds ratio (OR) 0.62, 95% credible interval 0.52, 0.74 and nintedanib OR 0.41, 95% credible interval 0.34, 0.51). In an indirect comparison, results indicate that nintedanib is statistically significantly better than pirfenidone in slowing FVC decline (OR 0.67, 95% credible interval 0.51, 0.88). Indirect comparisons of mortality were not statistically significant between the two therapies.

- 9.23. The Committee noted a systematic review and meta-analysis (Canestaro et al. Chest. 2016;149:756-66) reported that the central estimates for the comparison of all-cause mortality with control were consistent with a beneficial effect of pirfenidone and nintedanib, but that the credible intervals were wide and consistent with no effect. There was no evidence of a difference between nintedanib and pirfenidone, for respiratory specific mortality, all-cause mortality, and decline in percent predicted FVC.
- 9.24. The Committee noted the NICE UK recommendations for nintedanib include that the patient has a firmly established diagnosis of IPF, a FVC between 50% and 80% of predicted, that a price discount is applied and that treatment is stopped if the disease progresses in any 12 month period (defined as a confirmed decline in percent predicted FVC of 10% or more).
- 9.25. Members noted reports of clinical trials of nintedanib in the treatment of lung cancer, and considered there was risk of slippage if this product was to be used as adjunctive care for other treatments.
- 9.26. The Committee considered that there is a significant potential of misdiagnosis and patients being treated with nintedanib or pirfenidone inappropriately.
- 9.27. The Committee considered that nintedanib was not cost effective at the proposed price and, with the possibility of misdiagnosing IPF, could lead to a significant fiscal risk because it could be used in other fibrosing lung conditions. The Committee considered that the diagnosis of IPF would need to be made by a multidisciplinary team, with the Special Authority criteria similar to the source populations defined in the clinical trials, such as HRCT criteria or lung biopsy
- 9.28. Members also considered there was substantial risk with slippage and that a Special Authority would need to exclude patients who had a poor prognosis, and those with more stable long-term disease, as there was insufficient evidence of benefit with treatment.
- 9.29. The Committee recommended nintedanib be listed cost-neutral to pirfenidone (if pirfenidone is listed) and that if there is a continued decline of >10% in any 12 month period following treatment initiation, treatment should be stopped.

10. Pneumococcal vaccine for people with chronic autoimmune and rheumatic conditions on treatment with biologic disease modifying agents

Application

- 10.1. The Committee considered a submission from the New Zealand Rheumatology Association for the funding of pneumococcal vaccine (PPV23) for people with chronic autoimmune and rheumatic conditions on treatment with biologic disease modifying agents.

Recommendation

- 10.2. The Committee **recommended** the application to fund pneumococcal vaccine (PPV23) for people with chronic autoimmune and rheumatic conditions on treatment with biologic disease modifying agents, be declined.

- 10.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 10.4. The Committee noted that the applicant was requesting vaccination with PPV23 for patients with chronic autoimmune and rheumatic conditions on biologic disease modifying agents adalimumab, etanercept, infliximab, rituximab, and tocilizumab, plus disease modifying agents (DMARDs) methotrexate, leflunomide, sulphasalazine, hydroxychloroquine, plus corticosteroids “– all in various doses and combinations to control arthritis and prevent joint deformities and ultimately disability”. The Committee noted that the application did not explicitly exclude patients receiving low dose and/or short-course corticosteroid treatments, and did not include the use of PPV23 for other conditions nor the use of other vaccines for patients with chronic autoimmune and rheumatic conditions using DMARDs.
- 10.5. The Committee noted that it had previously considered applications for the use of PPV23 for vaccination against pneumococcal disease in people over the age of 65 years on two occasions (February 2014 and August 2015), and had declined both applications.
- 10.6. The Committee noted that there have been significant reductions in the incidence of invasive pneumococcal disease (IPD) in the vaccine eligible age groups in New Zealand since the introduction of a pneumococcal vaccine into the National Immunisation Schedule in 2008. The Committee noted for example there had been 445 cases reported in 2015 of IPD in people over the age of 5 years compared with 517 in 2008.
- 10.7. The Committee noted a retrospective review of patients who had received anti-TNF therapy for chronic autoimmune and rheumatic conditions at Counties Manukau DHB from May 2006 to April 2013 (Al-Majmoui et al., unpublished) (included in applicant's submission), had reported the rate of lower respiratory tract infections in these patients to be 5.7 per 100 patient years, being significantly higher than the 0.7 per 100 patient years reported by Burmester et al. (*Arthritis Res Ther.* 2014;16:R24). The Committee noted that there is an increased health need in this patient group, but considered that this health need would not be met by this proposal. The Committee noted a retrospective cohort study by Wotton & Goldacre (*J Epidemiol Community Health.* 2012;66:1177-81), using English linked hospital episode statistics, reporting a rate ratio (RR) for risk of invasive pneumococcal disease of 2.48 (95%CI 2.42-2.53) in patients with rheumatoid arthritis compared with a control population, with similarly high or higher RRs for other immune-modulated diseases (polyarteritis nodosa, systemic lupus erythematosus, autoimmune haemolytic anaemia, scleroderma, Addison's disease, diabetes mellitus, multiple sclerosis, primary biliary cirrhosis, Sjogren's syndrome, Crohn's disease).
- 10.8. The Committee noted that in a population based surveillance study Shigayeva et al (*Clin Infect Dis.* 2016;62:139-47) reported 28% of IPD episodes occurring in patients immunocompromised by underlying disease or medical treatment (including cancer, HIV infection, solid organ and stem cell transplant, sickle cell disease, chronic renal failure requiring dialysis, systemic immune diseases, asthma, rheumatoid arthritis, and chronic obstructive pulmonary disease), despite this group comprising but 2.8% of the study population, giving an average incidence rate ratio of IPD in immunocompromised persons 12-fold that of immunocompetent people; specifically for persons chronically receiving immunosuppressive medication for rheumatoid arthritis the incidence rate was 2.1 (95% CI 1.1-4.0).
- 10.9. The Committee noted the World Health Organization (WHO) report on pneumococcal vaccines had noted that polyvalent pneumococcal vaccine has an average protective efficacy of 60-70% in adults, but people who are immunodeficient or have chronic health conditions do not consistently develop immunity. The Committee also noted that the European League Against Rheumatism (EULAR) advises that clinicians should strongly

recommend PPV23 for patients with autoimmune inflammatory rheumatic diseases, as these patients are at increased risk of dying from pulmonary infections compared with the general population, with pneumococci being considered to be one of the main causative pathogens. The Committee noted EULAR considered that pneumococcal vaccine induces an adequate to slightly reduced humoral response in patients with rheumatoid arthritis.

- 10.10. The Committee noted that the immunogenicity of polysaccharide pneumococcal vaccine in patients with chronic rheumatic or autoimmune disease has been reviewed only in small studies. The Committee noted a review by Gluck and Muller-Ladner (Clin Infect Dis. 2008;46:1459-65) which summarised a number of studies and concluded that conventional DMARDs, such as methotrexate or azathioprine, appear to have only modest impact on post-vaccination titres. The review reported that, in general, 20% – and in some studies up to 50% – of patients do not develop protective antibody levels. Members also noted the review considered that among the newer, “biological” DMARDs, TNF antagonists appear to only slightly diminish antibody responses to vaccines, in contrast to preliminary data for rituximab indicating that it may have the potential to blunt immune responses, and concluding that more studies of these agents are urgently needed.
- 10.11. The Committee considered that while the application was for vaccination with PPV23, it is most likely that a PCV vaccine would be given at least 8 weeks prior to the PPV23, as is the case in other immunocompromised patients, this would result in an increase in cost of the proposal
- 10.12. The Committee noted that while the applicant considered there may be 1000 patients eligible for treatment, dispensing data showed there were about 4,700 arthritis patients on adalimumab and etanercept, and taking into account the total number of patients dispensed disease modifying drugs, the total population could be as high as 36,000. The Committee considered it would be difficult to fund only the RA patients when there are other patient population groups whose health needs may be similar if not higher.
- 10.13. The Committee considered that vaccination with PPV23 is well tolerated with few safety concerns, however the benefit remains uncertain in immunocompromised patients. The Committee considered there was no direct data contained in the application that demonstrated vaccination in this group of patients to be beneficial and cost effective.
- 10.14. The Committee recommended the application be declined.

11. Ciclosporin eye ointment for keratoconjunctivitis sicca and atopic and vernal keratoconjunctivitis

Application

- 11.1. The Committee considered an application from PHARMAC staff for topical ophthalmic ciclosporin eye preparations for the treatment of keratoconjunctivitis sicca, atopic and vernal keratoconjunctivitis sicca.

Recommendation

- 11.2. The Committee **recommended** ciclosporin 0.05% preparation be funded on the Pharmaceutical Schedule for the treatment of severe keratoconjunctivitis sicca with a low priority with the following amended Special Authority:

Severe keratoconjunctivitis sicca:

Initial application only from an Ophthalmologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has severe secretive tear deficiency disease with a DEWS grading of 3;
2. Evaporative tear deficiency has been excluded;
3. Patient must be responsive to ophthalmic corticosteroids and requires daily treatment with ophthalmic corticosteroids for more than 6 weeks;
4. Patient has developed glaucoma, or increased intra-ocular pressure requiring treatment, secondary to low dose ophthalmic corticosteroids;
5. Patient must have trialled a 2 month course of vitamin A eye ointment;

Renewal criteria: Ophthalmologists and optometrists valid for 6 months

Both:

1. Patient has responded; and
2. Return of intraocular pressure to baseline or acceptable level, and
3. To be used for a maximum of 2 years treatment.

- 11.3. The Committee **recommended** ciclosporin preparation at a strength higher than 0.05% be funded on the Pharmaceutical Schedule for the treatment of severe vernal or atopic keratoconjunctivitis sicca with a high priority with the following amended Special Authority:

Severe AKC/VKC

Initial application only from an Ophthalmologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has severe atopic keratoconjunctivitis/vernal keratoconjunctivitis; and
2. Any of the following:
 - 2.1 Corneal epithelium breakdown; or
 - 2.2 Progressive limbus thickening/hypertrophy; or
 - 2.3 Steroid induced intraocular pressure rise; or
 - 2.4 Requiring longer than 6 weeks of continuous steroid therapy.

Renewal criteria: Only from an ophthalmologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Treatment remains appropriate and is benefitting from treatment
2. Treatment has resulted in a reduction in the usage of ocular steroids from baseline,
3. The patient has experienced a 75% improvement in objective and subjective symptom measure from baseline.
4. There has been an improvement corneal epithelium measure from baseline

Discussion

- 11.4. The Committee noted that ciclosporin ophthalmic preparations had been reviewed by the Ophthalmology Subcommittee at their May 2010 and February 2016 meetings for patients with severe dry eye disease (keratoconjunctivitis sicca) and severe atopic and vernal keratoconjunctivitis. Members noted there has been a steady increase of NPPA applications for these indications over the last few years.

Keratoconjunctivitis Sicca

- 11.5. The Committee noted dry eye disease/keratoconjunctivitis sicca was a prevalent disease affecting over 15% of people over the age of 50 years. The Committee noted that keratoconjunctivitis sicca is a broad term and noted the disease can be separated into evaporative and aqueous-deficient disease. Members considered ciclosporin would be clinically appropriate for the latter group, particularly in patients with Sjogren's disease, and non- Sjogren's with lacrimal and immune mediated damage.

- 11.6. Members noted that there several tests that could be performed to diagnose patients with severe dry eye disease and quantify disease severity, including Schirmer test, staining (TBUT, Tear Break Up Time), staining of the cornea, and subjective measures of ocular surface symptoms.

- 11.7. The Committee considered the grading of dry eye severity can be done using the International Dry Eye WorkShop 2007 (DEWS) grading system, where disease is graded from 1 to 4. Members considered that the patient group that would most benefit from treatment with ciclosporin would have dry eye severity of between grades 2 and 3. Members considered ciclosporin eye preparations would not be clinically appropriate for very severe patients, such as those with grade 4 disease. Members considered these patients are unlikely to respond the damage to the underlying pathology is beyond repair for this patient group. Members considered treatment effect would occur within 6 months, and studies showing treatment for 3 months or less by Chen M, et al. (J Ocul Pharmacol Ther. 2010;26:361-6) and Baiza-Dura'n L, et al. (Br J Ophthalmol 2010;94:1312-15) under did not show a strong clinical effect. Members also noted ciclosporin eye preparations was well tolerated in trials, with the most common side effect being stinging, irritation and burning.
- 11.8. The Committee noted a study by Sall et al. (Ophthalmology 2000;107:631) (n=877) a multi-centre, randomised, double-masked trial comparing two concentrations of ciclosporin ophthalmic emulsion to its vehicle. The trial was composed of two parallel trials with patients who were defined as moderate to severe (2-3 DEWS grading), with 31% of patients reported to have Sjogren's disease. Primary outcomes reported significant changes from baseline corneal staining in 0.05%, 0.1% and vehicle groups. The greatest improvements in symptom measures (corneal staining, Schirmer test values with anaesthesia, and improvements in blurred vision) were reported in the 0.05% group after 6 months follow-up; and both 0.05% and 0.1% groups reported greatest reduction in average daily use of artificial tears at 6 months from baseline compared to vehicle. Members noted 61/877 patients discontinued treatment because of adverse events.
- 11.9. The Committee noted a study by Rao et al. (J Ocul Pharmacol Ther. 2010; 26:157-64) (n=58) a single-centre trial, where moderate-severe (2-3 DEWS grading) were randomised into either artificial tears or ciclosporin 0.05% group for 12 months. Results at 12 months showed 18% in the control group improved to lower disease severity compared to 39% of the ciclosporin group (p=0.007). The Schirmer test score improvements were seen by 12 months were greater in ciclosporin 0.05% group than control, 9.8 ± 1.0 mm compared to 7.6 ± 1.1 ; $P < 0.001$, respectively. Other outcomes such as Tear Break Up Time, ocular staining, Ocular Surface Disease Index (OSDI) and Goblet density all showed favourable results for ciclosporin group at 12 months. No adverse events were reported other than discomfort upon installation.
- 11.10. The Committee considered vitamin A eye ointment would be effective in some patients, as evidenced by a study Kim et al. (Am J Ophthalmol. 2009;147:206-213) that compared vitamin A (retinyl palimate 0.05%) eye preparation and ciclosporin 0.05% eye preparation. Results reported vitamin A eye ointment was an effective treatment for keratoconjunctivitis sicca which showed significant improvements in blurred vision, tear-film Break Up Time, and Schirmer score values compared to control at two and three months from follow-up. Members noted vitamin A eye ointment is fully funded without restriction and considered patients should try vitamin A eye preparation before progressing to ciclosporin.
- 11.11. The Committee considered most patients would require 6 months of ciclosporin as an initial treatment, and long-term treatment would be for 1-2 years, with a maximum of 2 years. Members considered that treatment with ciclosporin eye preparation for 1-2 years would result in long-term benefit as evidenced in the 10-year follow-up study by Straub M, et al. (Br J Ophthalmol 2016). Members noted patients in the trial with moderate to dry eye disease were treated with ciclosporin 0.05% for at least 6 months, and those who had persistent dry eye syndrome were maintained on further treatment. Members noted after 10 year follow-up, the median duration ciclosporin treatment was 23 (7-51) months for groups, and all patients required prolonged treatment after the first 6 months. Results reported significant improvements in Schirmer test scores, Fluorescein staining, and Tear Break Up Time test scores at the end of 10 year follow-up.

- 11.12. The Committee considered that treatments for dry eye disease depended on the aetiology of disease and can include artificial tear substitutes (mainstay of treatment), topical anti-inflammatory agents, punctual plugs, systemic anti-inflammatories, tetracyclines, vitamin A eye ointment and surgery.
- 11.13. The Committee considered the patient group and fiscal risk for severe keratoconjunctivitis would be large if the group mostly likely to be benefit from ciclosporin could not be well defined. Members considered there may be some cost offsets with some reduced use in ophthalmic corticosteroids and lubricant eye drops, however many of these treatments would be still be used concomitantly with ciclosporin eye preparation.
- 11.14. The Committee considered PHARMAC staff should seek advice from the Ophthalmology Subcommittee at its next meeting for an estimate of patient numbers for this indication.

Vernal and atopic keratoconjunctivitis

- 11.15. The Committee noted both severe vernal and atopic keratoconjunctivitis were forms of allergic keratoconjunctivitis, and were sometimes associated with sight-threatening symptoms.
- 11.16. The Committee noted severe VKC was presented as chronic bilateral inflammation of the conjunctiva, and associated with a personal and/or family history of atopy. Attacks were commonly seasonal but perennial during chronic disease. Members noted symptoms presented as giant papillae, corneal scarring and ulceration. In 5-30% of cases, permanent changes to the ocular surface may occur (such as keratoconus, corneal ulcers and/or steroid-induced glaucoma or cataract), and often accompanied by permanent visual impairment.
- 11.17. The Committee noted VKC typically occurred in male adolescents with a general onset in the first decade and duration up to one decade. Members noted VKC was more prevalent in ethnicities from African, Arab and South American decent.
- 11.18. The Committee noted AKC was the bilateral inflammation of the conjunctiva and eyelids with a strong association with atopic dermatitis and other atopic conditions. It has many similarities to VKC, yet AKC is distinct in a number of ways. AKC is perennial with no gender predilection, and patients with chronic AKC disease present with dry eyes, corneal neovascularization, and sterile ulcers.
- 11.19. The Committee noted there was a wide range of strengths available, from 0.05% to 2% topical ciclosporin eye preparation that could be used for severe VKC and AKC. Members considered the 0.5% and stronger strengths of ciclosporin eye preparations would likely be more effective than weaker presentations. Members noted the lack of proprietary higher strength formulations, and considered the data available suggested strengths higher than 0.05% would be appropriate.
- 11.20. The Committee noted the stronger strengths were not commercially available and would need to be compounded by third party specialist pharmacies. Members considered that there would be uncertainty around supply due to the lack of a registered product and it would be difficult to contract a supplier as specialist third party pharmacies compounded it. Members also noted the 0.05% and 0.1% proprietary products were not registered in New Zealand, and were supportive of PHARMAC approaching a supplier to source a registered product.
- 11.21. The Committee noted three studies for the treatment of VKC by Pucci, N et al. (Int J Immunopathol Pharmacol. 2010;23:865-71); Ebihara, N et al. (J Ocul Pharmacol Ther. 2009;25:365-72); and Spadavecchia L, et al. (Pediatr Allergy Immunol. 2006;17:527-32. Members considered the evidence for ciclosporin eye preparation for VKC was of

moderate strength and weak in quality. Members considered strengths of 0.1% to 2% would be effective in reducing objective signs and symptoms such as conjunctival hyperaemia, giant papillae, nodules; and subjective signs and symptoms such as itching, photophobia, foreign body sensation and burning.

- 11.22. Members noted the study by Pucci, N et al. (2010) assessed the long-term safety and efficacy of topical cyclosporine 1 and 2% eye drops in 156 children with severe VKC followed up over a period of seven years. Members noted both strengths reported ocular objective scores significantly improved ($p < 0.001$) over the years when compared to the beginning and the end of each seasonal treatment period, except for the last year (year 7).
- 11.23. Members noted a prospective post marketing study by Ebihara, N et al. (2009) examining the effectiveness and safety of ciclosporin 0.1% eye drops (n=594) VKC and AKC followed up over 6 months. Members noted results reported all scores for symptoms and signs significantly decreased from month 1 through to 6 months of treatment for both VKC and AKC, with the proportion of patients with moderate or severe corneal involvement decreased from 21.6% to 8.6% for VKC and from 35.9% to 18.3% for AKC.
- 11.24. The Committee noted in a study by Spadavecchia L, et al. (2006) which compared cyclosporine 1.25% versus 1% eye drops in a double-blind trial one eye for 2 weeks, then an open trial was conducted during the next 3 months and 2 weeks. Members noted severity of subjective symptoms and objective signs were significantly decreased after 2 weeks, and 4 months, compared with those at baseline ($P < 0.001$), in both groups of children who received cyclosporine eye drops 1.25% and 1%, respectively.
- 11.25. The Committee noted evidence for ophthalmic ciclosporin use in AKC was limited. Members considered a Cochrane systematic review (Cochrane Database Syst Rev. 2012 Sep 12;9:CD009078) that assessed different strengths of ciclosporin eye preparations for AKC. The review did not conduct a meta-analysis due to significant variability between trials and mixed results.
- 11.26. The Committee considered funded alternatives included corticosteroids, ophthalmic mast-cell stabilisers, oral and topical antihistamines, and systemic immunosuppression such as oral ciclosporin or methotrexate would have a role in managing severe VKC and AKC.
- 11.27. The Committee noted that the renewal criteria proposed by the Ophthalmology Subcommittee would allow optometrists and ophthalmologists to continue treatment. Members noted these patients were not seen at primary care level and would be managed by ophthalmologists, and would not be seen by GP's or optometrists.
- 11.28. The Committee considered patient numbers for severe vernal and atopic keratoconjunctivitis would be fewer than those estimated by PHARMAC staff. Members considered number of patients per year for the total patient group of vernal and atopic keratoconjunctivitis could be in the range of 300-400, but those in the severe group would be around 100 per year.
- 11.29. The Committee considered the renewal criteria of AKC and VKC for criteria number 4. Members considered PHARMAC staff should seek the advice of the Ophthalmology Subcommittee to obtain a clearer definition of "objective and subjective symptom improvement" component.

12. Methylnaltrexone subcutaneous injection for the treatment of opioid-induced constipation in patients receiving palliative care

Application

- 12.1. The Committee considered a funding application from Link Pharmaceuticals Ltd for the funding of methylnaltrexone (Relistor) subcutaneous injection for the treatment of opioid induced constipation (OIC) in patients receiving palliative care.

Recommendation

- 12.2. The Committee **recommended** that methylnaltrexone be listed in Section B and Section H of the Pharmaceutical Schedule subject to restrictions limiting its use to the treatment of opioid induced constipation in patients receiving palliative care when oral and rectal treatments are ineffective or unable to be tolerated, with a high priority.
- 12.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 12.4. The Committee noted that OIC is a significant problem in patients receiving palliative care with published prevalence up to 95% (MacLeod et al. Palliative Care Handbook, 8th ed. 2016). The Phase I report of Assessment of Palliative Care need in NZ 2011 (Palliative Care Council of New Zealand. 2011. National Health Needs Assessment for Palliative Care Phase 1 Report: Assessment of Palliative Care Need. Wellington: Cancer Control New Zealand) reports an estimated prevalence in cancer patients to be 47%, versus 32% in non-cancer patients. The complications of constipation can be debilitating and cause additional pain and discomfort which are contrary to the goals of palliative care.
- 12.5. The Committee noted that patients receiving palliative care generally have a high health need and often have multiple comorbidities and are required to take many different medications. The Committee considered that constipation is a common problem in palliative care with many other potential contributory factors in addition to opioids.
- 12.6. The Committee noted that manual evacuation is the most invasive intervention required in the treatment of OIC, which carries a small risk of bowel perforation. The Committee noted manual evacuation is however now rarely required because of the standard clinical practice of starting oral stimulant laxatives coincident with starting opioid therapy.
- 12.7. The Committee noted that methylnaltrexone is a selective mu-opioid receptor antagonist which does not cross the blood-brain barrier and therefore, unlike naltrexone, it does not reduce the centrally-mediated analgesic effect of opioids.
- 12.8. The Committee noted that methylnaltrexone is given by a single subcutaneous injection on alternate days or as required and requires the administrator to draw up the required amount. This could lead to inadvertent dosage error and the Committee therefore considered training would be required for patients, carers or family. The Committee noted methylnaltrexone tablet formulations are available in overseas countries. The Committee considered that although the oral route may be a preferred, the oral formulation is not currently registered in New Zealand and has not been evaluated in any large randomised-controlled trials in the palliative care setting.
- 12.9. The Committee considered that families play a significant role in palliative care and in some situations this medication could reduce the requirement for family administration of rectal preparations which may be difficult for the family and humiliating for many patients. The Committee considered that in certain circumstances this was particularly burdensome on family members, in particular in relation to children. The Committee noted cultural issues may also influence the acceptance of rectal preparations administered by family caregivers. Members noted that many palliative patients would consider manual evacuation undignified and it is also associated with a significant level of discomfort.

- 12.10. The Committee noted that anecdotally a significant number of palliative patients were not comfortable self-administering rectal therapies or having family members do so. These patients would therefore require a registered nurse or carer to administer any form of rectal preparation. The Committee considered a subcutaneous injection could reduce the need for rectal preparations, and would be seen as desirable by many patients and their families. The Committee noted that a registered nurse or carer would be visiting the house of a patient in palliative care approximately three times per week, therefore the nursing costs associated with administration of methylnaltrexone would be minimised.
- 12.11. The Committee noted that there are multiple treatments listed for constipation on the Pharmaceutical Schedule, and that these can vary in price from a few cents for oral treatment up to \$2.50 for some enemas. The Committee considered that enemas are cheap and have well-established efficacy. The Committee considered that rectal enema preparations would be the most appropriate comparator for methylnaltrexone, however it was noted that in all the clinical trials provided in the submission the comparator was placebo. The Committee referred PHARMAC to the Canterbury DHB guidelines for use of sodium acid phosphate enemas in this setting.
- 12.12. The Committee reviewed all the evidence provided in the submission by the applicant but noted that papers provided with evidence for the use of methylnaltrexone in the setting of chronic non-malignant pain were not considered relevant to the application for the palliative care setting.
- 12.13. The Committee considered a phase III double blind, randomised, placebo controlled trial 'MNTX 301' (Slatkin et al. J Support Oncol. 2009;7:39-46) in 154 patients based in 17 US study sites. There were 3 phases of the trial: Phase one : a single dose SC injection (0.15mg/kg OR 0.3mg/kg OR placebo), Phase two: a 28 day open-label active treatment as required, Phase 3: a 3-month extension study for as required treatment). Baseline laxatives were continued during the study and rescue laxatives were not permitted either 4 hours before or after methylnaltrexone administration in double blind phase and the first open-label dose. 152 participants completed the double blind phase with 147 entering the open label phase; however less than half completed the open label extension mainly due to disease progression or death. The primary outcome was 4-hour laxation response rate during the double blind phase; patients requiring rescue laxation or disimpaction within 4 hours were considered non responders. The 4-hour response rates were 61.7% in the 0.15mg/kg group, 58.2% in the 0.3mg/kg group, and 13.5% in the placebo group ($p < 0.01$ for each methylnaltrexone dose versus placebo). Secondary outcomes were rescue-free laxation within 24 hours, improvement in Global Clinical Impression of Change (GCIC) scale, improvement in constipation distress, improvement on stool consistency, change in baseline pain score, opioid withdrawal signs/symptoms and adverse events. 24-hour rescue-free laxation rates were 68.1%, 63.6% and 26.9% for 0.15mg/kg, 0.3 mg/kg, placebo respectively ($p < 0.01$ for each methylnaltrexone dose versus placebo).
- 12.14. The Committee considered a phase III trial 'MNTX 302' (Thomas et al. N Engl J Med. 2008;358:2332-43) conducted in the US and Canada with 133 patients enrolled in a 2 week double blind, randomised, placebo-controlled trial with a 3-month open-label extension. Patients were randomised to 0.15mg/kg of methylnaltrexone or placebo for 2 weeks on alternate days. Baseline laxatives were continued, however no laxatives were permitted 4 hours pre/post the study drug. At day 8, if fewer than 3 rescue-free laxations had occurred the dose of methylnaltrexone was doubled to 0.3mg/kg. The open-label extension allowed as required dosing up to every 24 hours starting at 0.15mg/kg. Co-primary outcomes in the double blind phase were rescue-free laxation within 4 hours after the first dose (48% in the methylnaltrexone group vs 15% in the placebo group) and rescue-free laxation within 4 hours after 2 or more of the first four doses (52% in the methylnaltrexone group vs 8% in the placebo group; $p < 0.01$ for both comparisons). The open label extension part of the study reported similar rates of 45-58% in the methylnaltrexone group and 48-52% in the placebo group. At day 8, 20 of the 62 patients

increased their dose of methylnaltrexone to 0.3mg/kg. This group increased their 4-hour rescue-free laxation rate from 15% to 24%.

- 12.15. The Committee considered a meta-analysis by Candy et al. (Cochrane Database Syst Rev. 2011:CD003448) which updated conventional laxatives versus methylnaltrexone in palliative care settings; seven studies with 616 participants were included. In the combined methylnaltrexone analysis with 287 patients, methylnaltrexone significantly induced laxation at 4 hours versus placebo (OR 6.95; 95% CI 3.83-12.61). There was no difference in the proportion experiencing side effects, although more flatulence and dizziness was experienced by those given methylnaltrexone.
- 12.16. The Committee noted it had been provided with no RCT's comparing methylnaltrexone with rectal preparations and this would have been desirable to support the application.
- 12.17. The Committee noted that in the Earnshaw et al. 2010 post-hoc analysis of MNTX 302 (Aliment Pharmacol Ther. 2010;31:911–921), the manual disimpaction rate was 3.17% in the methylnaltrexone group compared with 7.04% in the placebo group.
- 12.18. The Committee considered the evidence for the effectiveness of methylnaltrexone in this setting to be of good strength and moderate quality, although, in terms of relevance, members did note that the studies involving methylnaltrexone did not compare it with rectal preparations and there were no studies from Australia or New Zealand.
- 12.19. The Committee considered the estimates provided by the applicant and by PHARMAC underestimated patient numbers potentially accessing treatment for the provided indication.
- 12.20. The Committee considered that the health benefits of this pharmaceutical would be reductions in median time to rescue free laxation, constipation-related distress, and in rectal interventions such as manual disimpaction.
- 12.21. The Committee considered that there was significant financial risk with an unrestricted listing and it would also be a challenge to limit this pharmaceutical to the palliative care setting.
- 12.22. The Committee noted that there would likely be a reduction in the number of nurse visits associated with the use of methylnaltrexone. The Committee noted approximately 50% of rectal medications were administered by a nurse, while methylnaltrexone was likely to be able to be administered by family members via an indwelling subcutaneous butterfly or similar device.
- 12.23. The Committee recommended, given the significant fiscal risks, that any restriction should be targeted to patients with OIC receiving palliative care when oral and rectal treatments are ineffective or unable to be tolerated. The Committee did not recommend restrictions on the prescriber type or treatment duration, noting that the patients in this setting have life-limiting disease noting insufficient evidence to restrict length or quantity of treatment.

13. Ivabradine for computed tomography coronary angiography (CTCA)

Application

- 13.1. The Committee considered a clinician application for ivabradine as a premedication prior to CT coronary angiogram, in patients who still have a heart rate greater than 65 beats per minute after taking metoprolol or in whom metoprolol is contraindicated.

Recommendation

- 13.2. The Committee **recommended** that ivabradine be listed with a high priority, on the Hospital Medicines List only, restricted to patients with a heart rate of greater than 70

beats per minute for those on a maximally tolerated dose of beta blocker or unable to tolerate beta blockers, and who are indicated for CTCA.

- 13.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 13.4. The Committee noted that ivabradine is registered with the Australian TGA, the European Medicines Agency and the FDA for the treatment of chronic stable angina and chronic heart failure. The Committee considered it would only be evaluating the use of ivabradine as a premedication in CTCA as this is what the current application requested, and it would not be discussing the evidence for the use of ivabradine for heart failure or angina.
- 13.5. The Committee considered that if this medication were to be listed in the Community Schedule, there would be considerable use of ivabradine for other cardiac indications and it would be difficult to restrict use of ivabradine to those patients undergoing CTCA.
- 13.6. The Committee noted that ivabradine is an oral heart rate lowering agent that selectively inhibits the cardiac pacemaker cells I_f current at the sinoatrial node, and does not appear to affect other physiological cardiovascular parameters. The Committee considered that these features of ivabradine's pharmacological profile indicated that it may be suitable for use as a premedication prior to CTCA.
- 13.7. The Committee noted that the applicant stated that CTCA was used in the outpatient setting in five public hospitals in New Zealand, and noted that three of these five hospitals are currently using CTCA in the acute setting. The Committee noted that patients presenting for CTCA with a heart rate greater than 65 bpm are currently prescribed a premedication of oral or intravenous metoprolol tartrate 30-60 minutes prior to the scan, and that metoprolol tartrate is contraindicated in asthma and hypotension. The Committee considered that many patients with asthma are able to tolerate metoprolol and that depending on the degree of hypotension, metoprolol may not be contraindicated. It considered that patients with a heart rate of greater than 65 beats per minute may well undergo CTCA, in preference to coronary angiogram, however the image quality may be inadequate. They considered that it was likely that these patients would be booked for a repeat CTCA or alternate screening or intervention procedures. The Committee considered the applicant's estimate that approximately 5% of patients with a heart rate of greater than 65 beats per minute may have an inconclusive CTCA, that would be rectified with additional heart rate lowering medication, to be reasonable.
- 13.8. The Committee noted that CTCA is a procedure that is done in low risk patients, and those of high risk would still undergo invasive coronary angiography where the likely lesion can be addressed. The Committee considered that the health need of patients with a low risk of coronary artery disease undergoing a CTCA was moderate, but that as a group, patients with cardiovascular disease have a high health need over their lifetime. The Committee noted that cardiovascular disease is a Māori health area of focus.
- 13.9. The Committee noted the most recent clinical guidelines (MJA 2012) and considered that these represented the gold standard for CTCA.
- 13.10. The Committee noted the following published articles:
- Adile et al. (Br J Radiol. 2012;85:e424-8)
 - Guaricci et al. (Int J Cardiol. 2013;168:362-8)
 - Swedberg et al. (Lancet. 2010 ;376(9744):875-85.)
 - Litt et al. (N Engl J Med 2012; 366:1393-1403)
 - Qiu et al. (Cardiology 2016; 135:133-140)
 - Celik et al. (J Cardiovasc Comput Tomogr. 2014;8:77-82)
 - Celik et al. (Acta Radiol. 2014; 55 676-681)

- Lambrechtsen and Egstrup. (Clin Radiol. 2013;68:1054-8)
- 13.11. The Committee noted that the clinicaltrials.gov trial registration site catalogued two further trials in train or awaiting publication: 'Comparison of efficacy of ivabradine versus metoprolol' (not yet recruiting) and 'Heart rate reducing therapy in cardiac CT using ivabradine and bisoprolol' (completed).
 - 13.12. The Committee considered that the trials by Guaricci et al. (2013) and Adile et al. (2012) were most relevant to the funding submission. Adile et al. (2012) was a prospective RCT undertaken in 100 consecutive patients who had been referred for CTCA as an outpatient procedure. The authors did not state whether this study had a masked design, or concealed or open allocation to treatment. Patients were randomised to premedication protocols of oral metoprolol 50 mg twice daily or ivabradine 5 mg twice daily, which were commenced at least 48 hours before their scheduled CTCA.
 - 13.13. Guaricci et al. (2013) was a prospective, concealed allocation, open-label RCT occurred in 259 patients referred for CTCA as an outpatient procedure. The population studied was those taking beta blockers chronically, and those who were not. Of the study population, 114 patients were taking beta blockers chronically. These patients were all switched to atenolol 50 mg twice daily five days prior to their scheduled CTCA for 'uniformity' in the chronic beta blocker group. Participants in each population (the beta blocker group, and those that did not take beta blockers) were randomised to ivabradine 7.5 mg, ivabradine 5 mg and a control group. Those in the intervention group took ivabradine twice daily for 5 days prior to CTCA.
 - 13.14. With regards to these trials, the Committee considered that it was difficult to determine whether the results were clinically relevant for reasons including: patients indicated for a CTCA were already likely to be taking beta blockers chronically; it is uncertain if patients had a CTCA or if the quality of the CTCA improved in patients prescribed ivabradine; and the dosing regimen for beta blockers prior to CTCA differs in clinical practice (beta blockers are often taken one hour prior to CTCA). Further, the Committee were uncertain whether the image quality of the CTCA in patients taking ivabradine as a premedication altered their course of treatment or health outcomes. The Committee considered that the evidence reviewed demonstrated that ivabradine was more effective at lowering heart rate, compared to beta blockers.
 - 13.15. The Committee considered that there was a lack of published evidence that demonstrated an improvement in the quality of the CTCA after heart rate lowering with ivabradine, and that there was a lack of evidence showing how many more patients received a CTCA following premedication with ivabradine. The Committee considered that the strength of the evidence was reasonable and the quality of the evidence was reasonable.
 - 13.16. The Committee noted that the application was for a dose of 7.5 mg stat prior to CTCA, and noted that the evidence it reviewed included trials with a range of dosing regimens. Given the available evidence, the Committee considered that ivabradine could be dosed at a higher dose than the 7.5 mg stat that the applicant requested, and considered that the ivabradine dosing regimens in Adile et al. (2012) and Guaricci et al. (2013) reported a statistically significant decrease in patients heart rate prior to CTCA. The Committee considered that they could not recommend a specific dosing regimen based on the available evidence.
 - 13.17. The Committee considered that the number of CTCAs would be likely to increase if ivabradine was available, and noted and agreed with PHARMAC staff's estimate of these patient numbers and costs.
 - 13.18. The Committee considered that ivabradine as a premedication prior to CTCA will not impact the health need or health benefit to the family, whanau and wider society. The Committee noted that the listing of ivabradine for use as a premedication prior to CTCA

is unlikely to impact on the health outcomes of population groups experiencing health disparities.