

## **PTAC meeting held on 10 & 11 August 2017 (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. Correspondence and Matters Arising**

### **Melatonin for secondary insomnia in people with neurodevelopmental disorders 19 years of age and older**

- 1.1. The Committee noted that melatonin was funded from 1 July 2017 for children and adolescents aged 18 years and under with insomnia secondary to a neurodevelopmental disorder. The Committee noted that PHARMAC had received responses to consultation on the proposed funding of melatonin for this patient group that requested removal of the age limit from the funding restrictions, and that the Committee's advice was now sought on this matter.
- 1.2. The Committee reviewed the consultation responses and members noted that they were sympathetic to the viewpoint that patients should be able to continue a treatment that is providing benefit to them. Members acknowledged that neurodevelopmental disorders follow varying courses, for many patients extending into adulthood, and that arbitrary age cut-offs do not align with biological continua.
- 1.3. However, the Committee noted that melatonin is a relatively expensive treatment with a high fiscal risk if access was widened. Conversely the Committee also noted that currently funded agents such as benzodiazepines and zopiclone are associated with a potential risk of dependence and addiction.
- 1.4. The Committee noted that there do not appear to be any published clinical trials on the use of melatonin in patients with insomnia secondary to a neurodevelopmental disorder where the trial participants were aged 19 years and older. As such, the Committee considered that, at present, there is no good evidence to support either the initiation of melatonin for this indication in patients aged 19 years or older or the continuation of melatonin beyond 19 years in patients who were initiated on it under the age of 19 years. The Committee recommended that the funding criteria (Special Authority and Hospital Restrictions) for melatonin not be amended at this time.
- 1.5. The Committee noted that it would be willing to reassess this recommendation should supporting evidence become available on the use of melatonin for patients with insomnia secondary to a neurodevelopmental disorder in patients aged 19 years or older.

### **Cochrane Review of Direct Acting Antivirals for the treatment of chronic hepatitis C**

- 1.6. The Committee considered a recent Cochrane review on direct-acting antivirals (DAAs) for chronic hepatitis C (Jakonsen et al. Cochrane Database of Systematic Reviews. 2017: CD012143).
- 1.7. The Committee considered that SVR12, defined as a sustained virological response at 12 weeks, and used in clinical trials as a primary efficacy endpoint, was a good surrogate to determine hepatitis C virus cure rates in clinical trials, and correlated with clearance of the virus at 24 weeks post treatment (Yoshida et al. Hepatology 2015;61:41-5).
- 1.8. The Committee noted that early data suggests that achievement of SVR12 reduces the rates of hepatocellular carcinoma, decompensated liver disease and the requirement for liver transplant. The Committee agreed that long-term follow up data on the ability of DAAs to reduce chronic hepatitis C induced morbidity and mortality does not yet exist, and looked forward to reviewing this evidence once it becomes available.

### **Tiotropium Bromide**

- 1.9. The Committee noted the correspondence from Boehringer Ingelheim regarding the May 2017 PTAC minute for tiotropium for the treatment of severe asthma in adults, requesting the redaction of paragraphs 14.15 to 14.17, which related to the safety of tiotropium

Respimat in the COPD setting (but by extension relevant also to considering the use of tiotropium Respimat in severe asthma). The Committee noted that the references provided by Boehringer Ingelheim in its correspondence (Halpin et al. Int J COPD 2015;10:239-59; Karner et al. Cochrane Database of Systematic Reviews 2014: CD009285; Wise et al. N Engl J Med 2013;369:1491-501) had already been reviewed at past PTAC meetings, as part of informing PTAC's past considerations and recommendations, and that this material had been made available again to the Committee for consideration.

- 1.10. The Committee noted Boehringer Ingelheim's concerns regarding publication of the May 2017 minute in its current state, and considered that sufficient information had been recorded in the minute (namely the primary references), such that any interested party (clinician or patient) sufficiently concerned about the results reported in the papers reviewed by PTAC, and summarised in the minutes, could access the evidence themselves and conduct their own literature search or discuss with their health-care practitioner or content expert.
- 1.11. The Committee considered that the minute in its current state represented a factual summary of relevant papers that were reviewed and the discussions that took place at the May 2017 meeting. The Committee therefore did not consider that any redaction or amendment to the May 2017 PTAC minute for tiotropium for the treatment of severe asthma in adults was necessary. ([Appendix 1 full May Minute 2017 Tiotropium Minute](#))
- 1.12. The Committee noted that Medsafe is the medicines regulatory authority in New Zealand, and considered that its recommendation to write to Medsafe had been, and remained, reasonable and appropriate. The Committee considered that Medsafe can review the relevant literature and would reach its own conclusions as to whether the datasheets should be amended or remain unchanged.

#### **Anti-VEGF agents for the treatment of wAMD and DMO**

- 1.13. The Committee noted correspondence received from Bayer regarding the May 2017 PTAC minutes for anti-VEGFs for the treatment of wet age related macular degeneration (wAMD) and diabetic macular oedema (DMO), requesting amendments to paragraphs 13.7, 13.10, 13.13, 13.20, 13.22, and 13.40 and redaction of paragraphs 13.12, 13.19, and 13.29.
- 1.14. The Committee noted Bayer's comment regarding paragraph 13.13 of the May 2017 minute. The Committee noted the 6-month interim analysis of the PERSEUS trial (C Framme 2016, Poster presentation, EURETINA), which described 318 of the 632 patients included in PERSEUS as being treatment naïve, and that the minute had described all patients in PERSEUS as being treatment naïve. The Committee however considered that this did not change the uncertainty of the likely benefit of aflibercept if used in New Zealand, as the 6-month interim analysis of PERSEUS reported that changes in visual acuity in pre-treated patients ( $\geq 70$  letters from 22.9% to 25.8%) were considerably lower than in the treatment naïve patients ( $\geq 70$  letters from 24.8% to 34.0%). The Committee considered that paragraph 13.13 of the May 2017 minute should be corrected to reflect this (additions in bold, deletions in strikethrough):

"13.13 The Committee noted the new evidence provided by the supplier of aflibercept, Bayer. The Committee noted the longer-term data from the VIEW1 trial (Kaiser et al, Ophthalmology Retina 2017; 1: 304-13) as well as a post-hoc analysis of VIEW1 and VIEW2 trials (Jaffe et al, Ophthalmology 2016;123:1856-64). The Committee noted that both the VIEW1 and VIEW2 studies have previously been considered by PTAC, and noted that patients in those trials were treatment naïve, and have different characteristics to the population likely to receive treatment with aflibercept in New Zealand. The Committee therefore considered the applicability and generalisability of those trial results to the New Zealand setting is limited. The Committee noted interim results from two ongoing

real world observational studies provided by Bayer (RAINBOW and PERSEUS, unpublished data provided by supplier) which compared the effectiveness and injection frequency with what was observed in the results of the VIEW1 and VIEW2 studies. The Committee noted that ~~these trials were the RAINBOW trial~~ **was also conducted in treatment naïve patients and approximately half of patients in the PERSEUS trial were treatment naïve, and therefore considered that their relevance to the New Zealand setting is uncertain.**"

- 1.15. The Committee considered that other than the point above, the minute was an accurate reflection of the evidence that was reviewed and the discussions that took place in the meeting, such that no redactions and no other amendments were considered necessary. ([Appendix 2 Amended May Minute 2017 Anti VegF minute](#))

## **Elbasavir and Grazoprevir**

- 1.16. The Committee reviewed supplier correspondence that was submitted in relation to its review of elbasvir/grazoprevir (Zepatier) for the treatment of Hepatitis C genotypes 1 and 4 at the May 2017 PTAC meeting, requesting amendments to paragraphs 8.5, 8.6, 8.8, 8.12, 8.15.
- 1.17. The Committee noted that the supplier clarified that the secondary application for Zepatier was for the people who inject drugs or who remain unsuitable for treatment with Viekira Pak, not people failed by Viekira Pak, as indicated in the minutes. Members recommended that the minute should be corrected to reflect this.
- 1.18. Members noted the suppliers comment regarding paragraph 8.6 that suggested that it is not appropriate to compare treatments that were not evaluated against one another in a clinical trial. Members considered that, in the absence of a head to head trial, it is reasonable to compare outcomes in treatment arms, taking into account the described trial populations.
- 1.19. The Committee note that the statement in paragraph 8.8 regarding the percentage of genotype-1 infected patients without prior exposure to NS5A inhibitors that have detectable HCV NS5A resistance-associated variants is taken directly from the American Association for the Study of Liver Diseases HCV Guidance for Genotype 1 (<http://www.hcvguidelines.org/treatment-naive/gt1> accessed 6 August 2017).
- 1.20. Members note that while Viekira Pak is not registered for treatment of genotype 4, it would be expected that prescribers discuss this with their patients if they should choose to use the medication for treatment of this genotype; as per Section 25 of the Medicines Act 1981.
- 1.21. The Committee considered that other than the point above, the minute was an accurate reflection of the evidence that was reviewed and the discussions that took place in the meeting, such that no redactions and no other amendments were considered necessary. ([Appendix 3 Amended May Minute 2017 Elbasavir and Grazoprevir](#))

## **2. Subcommittee Minutes**

### **Nephrology Subcommittee**

- 2.1. The Committee noted the complete record of the Nephrology Subcommittee meeting held on 6 December 2016 and that paragraphs 7.11-7.19 (cinacalcet) and item 10 (enoxaparin) had previously been reviewed and accepted by the Committee at the May 2017 PTAC meeting.
- 2.2. The Committee noted and accepted recommendations related to paragraph 8.2.

- 2.3. The Committee noted and accepted paragraphs 4.19-4.23 regarding mycophenolate and its inclusion in the annual tender. Members noted that mycophenolate is not a narrow therapeutic index medicine and a brand change should be possible in this market. PHARMAC staff noted that alternative commercial strategies such as Request for Proposals would allow more flexibility regarding transition requirements if any brand change occurred.
- 2.4. The Committee noted paragraphs 7.2-7.10 in Matters Arising regarding immunisations in patients with renal disease and did not accept the recommendation in paragraph 7.10. The Committee noted the advice provided by the Nephrology Subcommittee regarding widening access to hepatitis B vaccine, pneumococcal vaccine and zoster vaccine was referred back the Immunisation Subcommittee at their recent meeting in July 2017 and would be considered by PTAC with the Immunisation Subcommittee minutes at the November 2017 PTAC meeting.
- 2.5. The Committee noted that the Subcommittee did not provide any advice regarding the use of the human papillomavirus vaccine (Gardasil 9) in the renal patient population and this should be assessed. The Committee recommended that the use of HPV vaccine in patients with CKD 5 or on dialysis be referred to the Immunisation Subcommittee for consideration at their next meeting. The Committee also recommended that the Immunisation Subcommittee and the Transplant Immunosuppressant Subcommittee consider the use of the HPV vaccine in patients pre/post transplantation who are over 26 years of age and are not currently funded. Members noted that the risk of cancer in this patient group is a relevant issue to consider.
- 2.6. The Committee noted there was an error in the minutes within paragraphs 7.2 and 7.6 regarding the units for estimated Glomerular Filtration Rate and this should be corrected in the Nephrology Subcommittee minute to state ml/min/1.73m<sup>2</sup>.
- 2.7. The Committee noted item 9 regarding the clinician funding application for tolvaptan for patients with autosomal dominant polycystic kidney disease. The Committee noted the high health need of this patient group and the lack of other treatments available. Members noted the data was very early and still developing. The Committee did not accept the recommendation from the Subcommittee and noted that consideration of funding tolvaptan should follow the usual PHARMAC process of Medsafe approval and a funding application from the supplier for review by PTAC.

### **Cancer Treatment Subcommittee**

- 2.8. The Committee noted the record of the Cancer Treatments Subcommittee of PTAC held on 24 March 2017.
- 2.9. Regarding item 5, dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy, the Committee noted that at its meeting in May 2013 it had recommended that funding for dexrazoxane for patients not participating in clinical trials be declined. The Committee acknowledged the Subcommittee's view and considered that the recently published evidence for the use of dexrazoxane should be reviewed by PTAC.
- 2.10. Regarding item 6, pembrolizumab for advanced non-small cell lung cancer (NSCLC), the Committee noted that at its meeting in May 2017 PTAC had deferred making a recommendation regarding the funding of pembrolizumab as a first-line treatment for patients with PD-L1 positive NSCLC pending publication of mature survival data and further information regarding the use of PD-L1 expression as a biomarker. The Committee noted that no additional information had been considered by the Subcommittee and reiterated its recommendation to defer making a recommendation on the use of pembrolizumab in previously untreated patients until the requested information had been reviewed by PTAC. The Committee noted and agreed with the remainder of this item and accepted the Subcommittee's recommendation regarding pembrolizumab for the second or third-line treatment of patients with previously treated advanced NSCLC whose tumours express PD-L1 at a level of 1% or greater.

- 2.11. The Committee noted and accepted the remainder of the record of the meeting.
- 2.12. The Committee noted that one of the founding members of the Cancer Treatments Subcommittee, Dr Vernon Harvey, had retired from the Subcommittee following the March meeting. The Committee acknowledged the significant contribution Dr Harvey had made over his time as a Subcommittee member.

### **Reproductive and Sexual Health Subcommittee**

- 2.13. The Committee noted and accepted the minutes of the Reproductive and Sexual Health Subcommittee of PTAC meeting held on 10 April 2017, with the following exceptions.
- 2.14. The Committee noted item 3.3 about the risk of venous thromboembolism with third-generation combined oral contraceptives, and noted that the Subcommittee had asked PTAC to consider the de Bastos M et al. Cochrane Database Systematic Review 2014;3:CD010813, on this matter. The Committee noted the concerns of the Subcommittee, and noted that the desogestrel-containing oral contraceptive listed in the Pharmaceutical Schedule is not fully subsidised and its use is declining. The Committee considered that some of the prescribing may be primarily for acne rather than contraception. The Committee considered that the risks of third-generation oral contraceptives are well-described and acknowledged in the clinical community. On balance, the Committee considered that the prescribing of third-generation contraceptives is up to individual clinicians with the expectation that the decision is being made in consultation with the patient, with due consideration of the clinical risks and benefits. The Committee recommended that no further action be taken.
- 2.15. The Committee noted item 3.9 about the eligibility criteria for levonorgestrel intrauterine systems for women with clotting disorders or on anticoagulants. The Committee requested that consideration of widening the access criteria for these patient groups be discussed at a future PTAC meeting.
- 2.16. The Committee noted item 6 regarding funding applications for levonorgestrel intrauterine systems (LIUS) for contraception. The Committee requested that the applications be brought to the Committee for review so that the Committee could make an informed recommendation on the use of LIUS for contraception. The Committee noted the need for robust evidence demonstrating the unmet health need and clinical benefit of LIUS over existing funded contraceptives, particularly in relation to the large fiscal risk of increasing funded access to this therapy.
- 2.17. The Committee noted item 7 regarding the other LIUS funding applications for heavy menstrual bleeding, endometrial hyperplasia without atypia and endometriosis, and requested that these also be brought to the Committee.
- 2.18. The Committee noted item 9 regarding a funding application from a clinician for clindamycin 2% vaginal cream for the treatment of desquamative inflammatory vaginosis (DIV). The Committee noted that the Subcommittee recommended that clindamycin 2% vaginal cream be listed on the Pharmaceutical Schedule, with a high priority, for the treatment of DIV. The Committee requested that this application be referred to the Anti-Infective Subcommittee, in particular to seek its advice on the potential for antimicrobial resistance with topical use of clindamycin cream. The Committee recommended that this advice be taken to a future PTAC meeting.

## **3. Lenalidomide – Multiple Myeloma**

### **Application**

- 3.1. The Committee considered a funding application from Celgene Pty Ltd (Celgene) for lenalidomide for the treatment of newly diagnosed multiple myeloma who are ineligible for stem cell transplant.

### **Recommendation**

- 3.2. The Committee **recommended** that lenalidomide for the treatment of newly diagnosed multiple myeloma who are ineligible for stem cell transplant, be funded only if **cost-neutral** to the health sector, compared with bortezomib containing regimens, specifically CyBorD and BMP in the first-line setting.
- 3.3. The Committee **recommended** that the funding application be referred to the Cancer Treatments Subcommittee for further advice, particularly on the expected patient numbers, Special Authority criteria and the comparative health benefits and risks versus bortezomib-containing regimens.
- 3.4. The Committee **recommended** that the Cancer Treatments Subcommittee review the currently funded treatments for multiple myeloma and provide advice on the optimal place in therapy of emerging new treatment options, including whether the currently funded bortezomib or lenalidomide treatment lines would need to change, and the likely role of thalidomide-containing regimens if lenalidomide were funded for newly diagnosed multiple myeloma.
- 3.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### Discussion

- 3.6. The Committee noted that the currently registered multiple myeloma indications for lenalidomide are the treatment of newly diagnosed multiple myeloma in those who are ineligible for autologous stem cell transplantation and for the treatment of multiple myeloma in those whose disease has progressed after one therapy.
- 3.7. The Committee noted that lenalidomide is currently funded for multiple myeloma in the third-line relapsed/refractory setting and the second-line setting where the patient has developed significant peripheral neuropathy with either bortezomib or thalidomide.
- 3.8. The Committee noted a PHARMAC staff analysis of Special Authority data suggesting that approximately 80% of patients with newly diagnosed multiple myeloma are treated first-line with a subcutaneous bortezomib-containing regimen, most commonly with oral cyclophosphamide and oral dexamethasone (CyBorD/BCD/VCD) or oral melphalan and oral prednisone (BMP/VMP).
- 3.9. The Committee noted that particularly in those who are ineligible for autologous stem cell transplantation, thalidomide-based regimens may be used, most commonly in combination with oral cyclophosphamide and oral dexamethasone (CTD) or oral melphalan and oral prednisone (MPT). The Committee considered that bortezomib-containing regimens are likely to remain the preferred option in this group if the treatment is expected to be tolerated and the weekly subcutaneous schedule of bortezomib is feasible. The Committee noted the Australian Clinical Practice Guidelines for Multiple Myeloma (Medical Scientific Advisory Group to the Myeloma Foundation of Australia, v4, March 2017), which references studies about bortezomib-containing regimens as the first-line treatment in transplant ineligible populations and states that MPT should only be used if lenalidomide or bortezomib combinations are contraindicated.
- 3.10. The Committee considered the potential suitability benefit of the proposed lenalidomide treatment regimen that consisted only of oral tablets, but also noted that subcutaneous bortezomib-containing regimens were easy to administer, albeit in an outpatient setting. The Committee noted that lenalidomide access was by restricted distribution program (i-access®). Only physicians and pharmacists registered with this program can prescribe and dispense the product to patient who meet the conditions. The Committee noted PHARMAC staff's view that whilst this programme increases the administrative burden of prescribing and dispensing, it was not placing undue barriers on access.
- 3.11. The Committee noted the FIRST (MM-020) large open-label randomised trial (Benboubker et al. N Engl J Med. 2014;371:906-17) which assigned 1623 eligible patients

- with previously untreated, symptomatic, and measurable multiple myeloma and who were ineligible for stem-cell transplantation to three treatment arms in a 1:1:1 ratio. The median age was 73 with about 53% male, mainly white ethnicity and 77% had an ECOG status 0 or 1. The treatment arms were lenalidomide and dexamethasone (Rd) in 28-day cycles until disease progression (535 patients), the same combination, but for a fixed course length of 72 weeks (18 cycles; 541 patients), and thalidomide with oral melphalan and oral prednisone (MPT) for 72 weeks (547 patients). The primary end-point was progression-free survival with continuous Rd versus MPT.
- 3.12. The Committee noted median progression-free survival was 25.5 months for continuous Rd, 20.7 months for 18 cycles of lenalidomide and dexamethasone and 21.2 months for MPT. Overall survival after three years was 59% and 56% in the Rd arms respectively and 51% in the MPT arm (median survival hadn't been reached by any group by four years). The Committee noted the proportion of patients with one or more adverse events of grade 3 or 4 was 85% in the continuous Rd group, 80% in the group that received 18 cycles of Rd, and 89% in the MPT group. Both Rd groups had lower rates of haematologic toxic events than the MPT group, but the incidence of grade 3 or 4 infection was increased with Rd.
  - 3.13. The Committee noted an abstract of the final analysis of overall survival from the FIRST trial (Facon T. ASH December 2016. Abstract 241). Median overall survival was reported as 59 months for continuous Rd, 62 months for 18 cycles of Rd and 49 months for MPT. Median progression-free survival was 26 months for continuous Rd, 21 months for 18 cycles of Rd and 22 months for MPT.
  - 3.14. The Committee noted the health-related quality-of-life evaluation of the FIRST study cohort (Delforge et al. *Haematologica*. 2015;100:826-33). The Committee noted the data was collected using validated questionnaires (QLQ-MY20, QLQ-C30, and EQ-5D), but considered the data was poorly reported in the paper. The analysis focused on the EQ-5D utility value and six domains pre-selected for their perceived clinical relevance in multiple myeloma.
  - 3.15. The Committee noted baseline EORTC-QLQ global health scores were about 51, and improved in both arms (both Rd arms combined) by about 5 units (100-point scale) after 18 months. The Committee noted both treatments appear to have a positive impact on QoL, but the Committee considered the very small relative changes in utility, on only some selected measurements, meant there was unlikely to be any meaningful quality-of-life difference between the treatments. The Committee noted the minimal important differences (MIDs) were established by calculating the standard error of measurement in a previous trial (Dimopoulos et al. *Haematologica*. 2013;98:784-8) and somewhat align with those established by Kvam et al (*Eur J Haematol*. 2010;84:345-53), although there does not appear to be any consensus in the literature that these are clinically significant (Nielsen et al. *Eur J Haematol*. 2017;99:3-17).
  - 3.16. The Committee noted a related open-label phase III trial (Durie et al *Lancet* 2017; 389: 519–27) which randomly assigned 525 eligible patients with previously untreated, measurable multiple myeloma who were not planned for immediate autologous stem-cell transplant to two treatment arms of Vd or bortezomib plus lenalidomide and dexamethasone (VRd) in a 1:1 ratio. The Committee noted that compared to FIRST, the participants were younger and fitter and many (about 70%) were considered transplant eligible. Median follow-up was 55 months. Median progression-free survival was significantly improved in the VRd group (43 months vs 30 months in the Rd group; stratified hazard ratio [HR] 0.712, 96% CI 0.56–0.906; one-sided p value 0.0018). The median overall survival was also significantly improved in the VRd group (75 months vs 64 months in the Rd group, HR 0.709, 95% CI 0.524–0.959; two-sided p value 0.025). All participants had VTE prophylaxis.
  - 3.17. The Committee noted a network meta-analysis indirectly comparing the first-line treatments for patients with multiple myeloma not eligible for stem cell transplantation

- (Weisel et al. *Leuk Lymphoma*. 2017;58:153-61). The Committee noted the considerable uncertainty in the comparison between VMP and Rd and that the upper confidence intervals were close to the null. In the full analysis, including all relevant linkable comparator trials, the hazard ratio for overall survival for Rd compared to VMP was 0.66 (0.46 to 0.93) and for progression-free survival was 0.70 (0.49 to 0.99). The Committee considered that this appears more optimistic than suggested by informal comparison of individual trial arms (including other intravenous bortezomib trials – Mateos et al. *Blood*. 2014;124:1887-93; Palumbo et al. *J Clin Oncol*. 2014;32:634-40; San Miguel et al. *J Clin Oncol*. 2013;31:448-55), where the median progression-free survival ranged from 56 to 63 months and overall survival ranged from 24 to 32 months.
- 3.18. The Committee noted a formal multistep pair-wise indirect comparison provided by the supplier using VISTA (San Miguel et al. *J Clin Oncol*. 2013;31:448-55) for the comparison of VMP and MP, with IFM 99–06 (Facon et al. *Lancet*. 2007;370:1209-18), IFM 01/01 (Hulin et al. *J Clin Oncol*. 2009;27:3664-70) and Sacchi et al. *Leuk Lymphoma*. 2011;52:1942-8 for the comparison of MP and MPT, then the FIRST trial above to compare MPT to Rd. The Committee noted the HR point estimates for progression-free survival and overall survival both numerically favour Rd but statistical significance was not met for progression-free survival, with the upper confidence interval reaching 1.0.
  - 3.19. The Committee noted that the MP arm in VISTA, which was used in the network meta-analysis and the supplier indirect comparison, reported a median overall survival of 43.1 months, which was considerably longer than median overall survival with MP in another MPT trial meta-analysis of 32.7 months (Fayers et al. *Blood*. 2011;118:1239-47). The Committee considered that this may mean that the efficacy of VMP is underestimated in the indirect comparison, potentially overestimating the comparative survival benefit of Rd.
  - 3.20. The Committee noted that from an annual incidence of around 350 patients, it was reasonable to suggest that all of those on non-bortezomib regimens (20%) and maybe half of those on bortezomib containing regimens would use continuous lenalidomide, however the Committee recommended that PHARMAC seek advice from CaTSoP on this aspect.
  - 3.21. The Committee considered that the FIRST randomised control trial was of good quality and provided strong evidence of a survival benefit for continuous Rd versus MPT. The Committee considered that the magnitude of the difference in quality of life measurements for Rd versus MPT was inadequate to place additional value on this aspect. At this time, the Committee considered a clinically significant difference in quality of life compared to bortezomib-containing regimens remains unknown, but would appear unlikely given the comparison with MPT.
  - 3.22. The Committee considered that there is considerable uncertainty whether Rd is more efficacious than the bortezomib-containing regimens. Despite the obvious limitations of indirectly comparing different study populations, the point estimates of survival outcomes in relevant trials appeared similar. On balance, at this time, in the absence of direct comparison evidence, the Committee considered it was reasonable to assume that lenalidomide- and bortezomib-containing Rd regimes had the same or similar efficacy in the first-line setting.

#### **4. Ivabradine – Chronic Heart Failure**

##### **Application**

- 4.1. The Committee considered an application from a group of cardiologists for the funding of ivabradine for heart failure for patients with chronic heart failure (NYHA class I-IV) with systolic dysfunction (LVEF  $\leq$ 35%) and in sinus rhythm with a heart rate  $\geq$ 75 beats per minute and on maximally tolerated heart failure therapy.

## Recommendation

- 4.2. The Committee **recommended** that the listing of ivabradine for heart failure for patients with Chronic heart failure (NYHA class II-IV) with systolic dysfunction (LVEF  $\leq$ 35%) and in sinus rhythm with a heart rate  $\geq$ 75 beats per minute and on maximally tolerated heart failure therapy be declined.
- 4.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

## Discussion

- 4.4. The Committee noted that ivabradine has been listed on the hospital medicines list (HML) since July 2017 for patients who are indicated for a CT coronary angiography and are intolerant to, or are on maximally tolerated beta blockers, with a heart rate of greater than 70 beats per minute. The Committee noted that an application for ivabradine for the treatment of inappropriate sinus tachycardia was reviewed by the Cardiovascular Subcommittee as a PHARMAC generated paper at its June 2012 meeting and given a high priority.
- 4.5. The Committee noted that ivabradine is not registered in New Zealand but that it is registered with the Australian TGA, the European Medicines Agency, and the FDA for the treatment of chronic stable angina and chronic heart failure. It noted that the innovator company had not yet sought registration in New Zealand and that although there were generic products available, none however were currently seeking registration in New Zealand.
- 4.6. The Committee noted that ivabradine lowers heart rate alone, without affecting blood pressure, cardiac output, myocardial contractility, coronary blood flow or interatrial, atrioventricular or intra ventricular conduction pathways, or ventricular repolarisation.
- 4.7. The Committee considered the references submitted as part of this application, including SHIFT, the pivotal trial for ivabradine (Swedberg et al. Lancet 2010;376:875-85), the post hoc analyses of the SHIFT trial (Böhm et al. Clin Res Cardio 2013;102:11-22, Böhm et al. Lancet 2010;376:886-94, Borer et al. Am J Cardio 2014;113:497-503, Borer et al. Eur Heart J 2014;33:2813-20, Swedberg et al. JACC 2012;59:1938-45). The Committee also reviewed the BEAUTIFUL trial (Fox et al. Lancet 2008;372:807-16). The Committee considered that the quality of the evidence for the pivotal trial was high, and that the post hoc analyses were of moderate strength.
- 4.8. The Committee noted SHIFT, a double blind, randomised, controlled trial of 6558 patients (n=3268 in the ivabradine group, n=3290 in the placebo group) with moderate-to-severe heart failure and left ventricular systolic dysfunction, who had been hospitalised for heart failure in the preceding year and were on a stable background guidelines-based treatment. The Committee noted that only 26% of patients in the SHIFT trial were taking the target dose of beta blocker with about 50% of the trial participants taking less than half of the target beta blocker dose, mainly due to hypotension, fatigue, dyspnoea and dizziness. The Committee considered that there was a significant reduction in the primary endpoint, a composite of cardiovascular death or hospital admission for worsening heart failure, which occurred in 793 patients in the ivabradine group and 937 patients in the placebo group (HR 0.82, 95%CI 0.75-0.90, p<0.0001), and considered that this reduction in the primary endpoint was reported to be mainly due to reductions in hospitalisations for heart failure. The Committee noted that the SHIFT trial did not report significant reductions in all-cause or cardiovascular mortality, but that the trial did report fewer hospital admissions for heart failure and fewer deaths due to heart failure. It considered that the SHIFT trial showed diminishing benefit in patients with lower baseline heart rates (less than 77 beats per minute). The Committee noted that the SHIFT trial reported that ivabradine was reasonably well tolerated, however members noted that there was a statistically significant number of adverse events such as symptomatic bradycardia, atrial fibrillation and visual disturbances. Based on this study, the Committee considered that

ivabradine could reduce hospital admissions for heart failure and deaths due to heart failure, in patients in sinus rhythm with a heart rate of greater than 70 beats per minute who are already on guidelines-based treatment. However, the Committee considered that preventing such hospital admissions did not alter distal outcomes, and that overall the evidence in the SHIFT trial did not support a mortality benefit for ivabradine.

- 4.9. The Committee noted Fox et al. (2008), a large multicenter, double blind, placebo controlled, randomised controlled trial in 10,917 patients with stable coronary heart disease and a left ventricular ejection fraction of less than 40%. 85% of the trial participants were taking beta blockers, however their doses were not reported. The Committee noted that this trial had a composite primary endpoint of cardiovascular death, hospital admission with myocardial infarction and hospital admission with heart failure. It considered that there was no improvement in cardiac outcomes in patients that were treated with ivabradine, and noted that patients in the subgroup with heart rates of greater than 70 beats per minute who were treated with ivabradine were reported to have reduced admissions for myocardial infarction and coronary revascularisation.
- 4.10. The Committee noted Böhm et al. (2013) a post hoc analysis of the SHIFT trial in patients with a baseline heart rate of greater than 75 beats per minute (4150 patients), and patients with a baseline heart rate between 70 and 74 beats per minute. The authors reported a reduction in the composite primary endpoint in the group with a baseline heart rate greater than 75 beats per minute, in particular reporting statistically significant reductions in all-cause mortality, cardiovascular mortality, heart failure death and heart failure hospitalisation. The Committee noted that the upper limit of the 95% confidence interval hazard ratio was close to one for cardiovascular mortality and all-cause mortality. The Committee noted that none of the end points were significantly reduced in the group with a baseline heart rate of 70 to 74 beats per minute. The Committee also noted interpreting these post hoc analyses was difficult without clear biological plausibility for the post hoc groups selected for analysis.
- 4.11. The Committee noted Böhm et al. (2010), a post hoc analysis of the SHIFT trial cardiovascular outcomes in the placebo group (3264 patients) and the ivabradine group (3241 patients), categorised by quintiles of baseline heart rate in the placebo group. The authors analysed the heart rate of the ivabradine group at day 28 in relation to cardiovascular outcomes. The Committee noted that patients with lower heart rates in the placebo group and the treatment group had fewer primary composite endpoint events than patients with higher heart rates.
- 4.12. The Committee noted Borer et al (2014), a post hoc analysis of the SHIFT trial population of cardiovascular outcomes in patients with severe systolic heart failure (defined as NYHA IV and left ventricular ejection function less than 20%). The authors reported a statistically significant reduction of the composite primary endpoint and secondary endpoints, except for hospitalisation for any cause, in the ivabradine group versus the placebo group in patients with severe heart failure and heart rates of greater than 75 beats per minute. They also reported that the degree of relative risk reduction was similar in patients with severe versus less severe heart failure, and that there was no difference in the safety profile in those with severe heart failure on ivabradine versus placebo.
- 4.13. The Committee noted Borer et al (2012), a post hoc analysis of the SHIFT population on recurrent hospitalisations for worsening heart failure. They considered that there were statistically significant risk reductions for the second and third hospitalisations for heart failure, all cause and cardiovascular admissions in the ivabradine versus the placebo group in patients with a heart rate of greater than 75 beats per minute.
- 4.14. The Committee noted Swedberg et al (2012), a post hoc analysis of the SHIFT population on the effect of beta blocker dose on ivabradine response. The authors reported that the composite primary endpoint was reduced in the ivabradine group in the subgroup where participants were taking less than 50% of the target beta blocker dose. For the other subgroups of beta blocker dose, the Committee noted that there was no significant

- treatment effect for increasing beta blocker dose and that the magnitude of heart rate reduction by beta blocker with ivabradine (rather than beta blocker dose alone) determined the effect on outcomes.
- 4.15. The Committee considered that the population that would benefit most from ivabradine would be those with a reduced ejection fraction (less than 35% on echocardiogram), NYHA II-IV, in sinus rhythm and a resting heart rate of greater than 75 beats per minute despite being on guideline directed heart failure therapy, including optimal dosing with a beta blocker, an ACE inhibitor or Angiotensin II inhibitor and a mineralocorticoid inhibitor. The Committee also considered that ivabradine is not indicated in atrial fibrillation, and so regular ECG monitoring would need to occur to indicate whether ivabradine should be stopped for patients who have persistent or permanent atrial fibrillation.
  - 4.16. The Committee considered that there was minimal benefit in taking ivabradine if a patient with heart failure was on optimally dosed beta blocker therapy. The Committee considered that despite many studies showing the tolerability of  $\beta$  blockers, (overall adverse event rates similar to those with placebo in trials), there remains reluctance to up-titrate  $\beta$  blockers to doses recommended in clinical trials.
  - 4.17. It considered that the mortality benefit was small, and that optimal treatment with a beta blocker was an appropriate alternative. The Committee considered that many of the side effects of ivabradine were similar to those of beta blockers e.g. bradycardia. Members considered that there could be an impact on the health sector, especially secondary care as there would need to be careful titration of ivabradine dosing and increased monitoring and treatment of side effects. The Committee considered that access to echocardiography differed around New Zealand and that this investigation is essential in differentiating heart failure with reduced ejection fraction from heart failure with preserved ejection fraction (and hence identifying the group of patients who might benefit from ivabradine).
  - 4.18. The Committee also considered that the uptake of ivabradine in Australia was not high, particularly due to polypharmacy and multi-morbidity in that group of patients. Members noted that there was no evidence of benefit for using ivabradine in heart failure with preserved ejection fraction, which was a common type of heart failure.
  - 4.19. The Committee further noted that treatment with beta blockers does result in other effects likely to contribute to their mortality benefit in patients with chronic heart failure with reduced ejection fraction, in addition to heart rate reduction alone; so Ivabradine is not an alternative to beta-blocker use in this indication.
  - 4.20. The Committee considered that there were no non-clinical features of this medicine which would impact on its use, however, it considered that the fact that there was no registered product in New Zealand to be a significant issue. They considered that whilst other treatments are available under section 29 of the Medicines Act 1982, these were usually for a small number of patients and a niche indication. The Committee considered that heart failure is a common disease and there are suitable funded alternatives furthermore, members considered the estimated NNT (to prevent one first HF hospitalization within 1 year) was 27(Rogers et al. Curr Med Res Opin. 2015;31:1903-9).
  - 4.21. Members considered that if ivabradine was to be listed on the Pharmaceutical Schedule it would need to be restricted via Special Authority to ensure that patients benefitting most would receive it. The Committee considered that a restriction would be particularly useful due to the high proportion of patients with heart failure not currently treated with optimal dosing of beta blockers.
  - 4.22. The Committee considered that the approximated cost utility analysis for the estimated pricing of ivabradine from the innovator indicated that ivabradine was unlikely to be cost effective. Members considered that the comparator for ivabradine would be standard heart failure care, as ivabradine would be used as an add-on therapy. The Committee considered

that the rates of heart failure with reduced ejection fraction reported in the literature (5-7% in Sweitzer et al Am J Cardiol. 2008;101:1151-6, and Cullington et al Heart 2011;97:1961-6) would be likely to be similar in New Zealand if ivabradine was initiated in secondary care (as opposed to primary care). However, it was likely to be higher if baseline resting heart rate was not measured by ECG and if the patient was not taking an optimal beta blocker dose. The Committee considered that the patient uptake numbers modelled by PHARMAC staff appeared reasonable.

- 4.23. In summary, the Committee recommended that ivabradine for heart failure should be declined for listing on the Pharmaceutical Schedule at this time, as it is currently not registered in New Zealand; would be used in a potentially large patient population, optimal dose beta blockers are a suitable funded alternative; and that currently a large proportion of patients are receiving suboptimal dosing of already-funded beta-blockers. In addition, the Committee considered that treatment with ivabradine added minimal therapeutic effect when patients are treated with optimal beta blocker dosing.

## 5. Adalimumab – Chronic Ocular Inflammation

### Application

- 5.1. The Committee considered a submission from AbbVie for widened access to adalimumab on Section B and H of the Pharmaceutical Schedule for the treatment of adults and children with severe or chronic non-infectious intermediate, posterior, and panuveitis who have had a poor response to corticosteroids.
- 5.2. Dr Rademaker participated in the discussion, but did not vote.

### Recommendation

- 5.3. The Committee **recommended** that access to adalimumab be widened for the treatment of severe and chronic ocular inflammation, subject to restrictions, with a low priority.
- 5.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### Discussion

- 5.5. The Committee noted that uveitis can broadly be categorised according to anatomical location of the inflammation as well as whether it is of an infectious or non-infectious origin. The Committee noted that non-infectious uveitis is thought to involve innate and adaptive immune systems with retinal damage mediated via a complex interaction between retinal antigens, T-cells, and pro-inflammatory cytokines (IL-1b, IL-6, TNF-alpha).
- 5.6. The Committee noted that adalimumab is a tissue necrosis factor (TNF) inhibitor, approved by Medsafe for the treatment of severe and chronic ocular inflammation, and is administered via subcutaneous injection. The Committee noted that another TNF inhibitor, infliximab, is currently listed with restrictions in Section H of the Pharmaceutical Schedule, and is used in hospitals for the treatment of severe and chronic ocular inflammation. The Committee noted that infliximab is administered as an IV infusion and is being used off-label for this indication. The Committee also noted it had never reviewed any applications for infliximab for uveitis, as infliximab's use in this setting was already established practice in hospitals before PHARMAC became responsible for management of the Hospital Medicines List.
- 5.7. The Committee noted within the range of non-infectious uveitis sub-types, the four anatomical classifications of uveitis are anterior, intermediate, posterior and panuveitis. The Committee noted that although anterior disease is the predominant form of uveitis accounting for approximately 50-60% of cases, complications associated with non-infectious intermediate, posterior and panuveitis account for most of the visual morbidity and blindness.

- 5.8. The Committee noted that uveitis in general can occur at any age, however it is most likely to affect individuals of working age. The Committee noted a New Zealand observational study by Wong et al 2016. (Ocul Immunol Inflamm 2016; Aug 18:1-7 <http://dx.doi.org/10.1080/09273948.2016.1203957Epub>) that reported the median age of disease onset was 42 years, with 77% of patients aged between 17 and 60 when their disease was diagnosed, and 4.6% of all cases being in children under 17 years of age. The Committee also noted that Wong et al 2016 did not show Māori populations to be disproportionately affected by uveitis compared to other ethnic groups.
- 5.9. The Committee considered that visual loss affecting people of working age would likely affect the health and general well-being of the family and whānau, particularly if the disease affects the person's ability to work or drive. The Committee noted Bambara et al, 2009 (Invest Ophthalmol Vis Sci 2009;50:1585-92) which identified that caregivers of visually impaired patients were at risk for depression, with the risk of depression being associated with younger caregiver age, female caregiver gender, younger age of the visually impaired person, and severity of the visual impairment.
- 5.10. The Committee noted a systematic review by Miserocchi et al (Eur J Ophthalmol 2013;23:705-17) which looked at the worldwide epidemiology of uveitis. The authors reported that in the developed world uveitis occurs with an overall incidence of approximately 17 and 52 per 100,000 in the population per year, resulting in a prevalence of about 38 to 714 cases per 100,000 in the population.
- 5.11. The Committee noted that non-infectious uveitis can affect one or both eyes, and goes through phases of active inflammation or flares - when patients are aware of ocular discomfort, pain, redness, blurred vision, dark floating spots (floaters), and visual loss separated by periods of variable length when the inflammation or flare has settled and the patient is asymptomatic. The Committee noted that on average, the duration of visual impairment associated with a flare is around 4 months per eye per year. The Committee noted that recurrent episodes of inflammation and flare result in cumulative damage, leading to significant complications such as cataracts, glaucoma, cystoid macular oedema, retinal detachment, visual loss and blindness.
- 5.12. The Committee noted that severe, non-infectious forms of uveitis are currently being treated with systemic corticosteroid therapy, however corticosteroids at the doses required to control inflammation are inappropriate for long-term use, as they are associated with a range of side effects including diabetes, osteoporosis, cataracts, glaucoma, Cushing's disease, and mood disorders. The Committee noted that conventional immunomodulatory therapies such as methotrexate, azathioprine, mycophenolate and ciclosporin are often used as a corticosteroid-sparing strategy. However, the Committee considered that many patients would still be unable to taper their steroid doses to a safe level without experiencing disease flare.
- 5.13. The Committee noted the evidence presented in the submission, including the two-pivotal double-blinded, phase III trials, VISUAL I (Jaffe et al, Ann Rheum Dis, 2015;74(Suppl 2):849-50) and VISUAL II (Nguyen et al, Lancet, 2016;388:1183-92) which studied the safety and efficacy of adalimumab versus placebo for the treatment of uveitis.
- 5.14. The Committee noted that VISUAL I (Jaffe et al, 2015) included patients over 18 years of age who had a diagnosis of active non-infectious intermediate, posterior, or panuveitis. Patients were randomised 1:1 to receive either adalimumab or matched placebo. All patients received high dose prednisolone (60 mg per day) at the start of the trial, and were mandatorily tapered off prednisolone by week 15. The primary endpoint was the time to treatment failure at or after week 6. The Committee noted that a total of 217 patients were included in the intention to treat analysis (n=110 in the adalimumab group, n=107 in the placebo group). The authors reported that median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were less

likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70;  $P < 0.001$ ).

- 5.15. The Committee noted that in VISUAL II (Nguyen et al, 2016) patients aged  $\geq 18$  years with inactive, non-infectious intermediate, posterior, or panuveitis, who were controlled on 10–35 mg/day of prednisone, were randomly assigned to receive either subcutaneous adalimumab or placebo. The trial protocol then required all patients to taper off prednisone by week 19. The primary efficacy endpoint was time to treatment failure. A total of 226 patients comprised the intention to treat population ( $n=111$  received placebo, and  $n=115$  received adalimumab). The authors reported treatment failure in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group. Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (median not reached [ $>18$  months] vs 8.3 months; hazard ratio 0.57, 95% CI 0.39 – 0.84;  $p=0.004$ ).
- 5.16. The Committee considered that the VISUAL I and VISUAL II studies were of moderate quality. However, the Committee noted that both VISUAL I and VISUAL II studies used a composite endpoint of time to treatment failure, and compared treatment with adalimumab to placebo. The Committee considered that the results of these studies suggested that adalimumab delivered improved composite end points compared to placebo, however the Committee did not think placebo was the appropriate comparator as current treatment in NZ for refractory patients is with infliximab.
- 5.17. The submission also included a number of studies comparing adalimumab to infliximab in the treatment of uveitis. The Committee reviewed the following studies in detail:
  - Martel et al, 2012 (Ocul Immunol Inflamm. 2012;20:18-26),
  - Mercier et al, 2016 (Ocul Immunol Inflamm. 2016;24:1-8),
  - Simionini et al, 2011 (Arthritis Care Res, 2011;63:612-8),
  - Vallet et al, 2016 (Arthritis Rheumatol. 2016;68:1522-30).
- 5.18. The Committee noted that all the above trials were retrospective cohort studies, and that most reported on small patient numbers (33 to 41 patients), apart from Vallet et al, 2016 which had recruited 160 patients. The Committee considered that infliximab and adalimumab had largely similar reported rates of response, rates of disease control, and reductions in steroid use, and that it would be reasonable to consider that adalimumab would be equally efficacious compared to infliximab. The Committee considered that the trials were of low quality and low strength due to heterogeneity of disease aetiology, prior therapies, outcome measures, and dosing regimens. However, the Committee considered that heterogeneity in uveitis trials were not uncommon and noted a systematic review by Denniston et al, 2015 (Orphanet Journal of Rare Diseases 2015;10:97) which describes the heterogeneity both in terms of the underlying disease (intermediate, posterior, and panuveitis) and the general lack of consensus regarding primary efficacy outcome measures.
- 5.19. The Committee noted the different method of administration for adalimumab, which is given as a subcutaneous injection, as opposed to infliximab, which is given as an IV infusion. The Committee considered that whilst infliximab may have a more rapid onset of action than adalimumab due to its method of administration, infliximab was associated with more adverse events such as infections, hypersensitivity reactions, autoimmune diseases, and injection site reactions. The Committee considered that safety of TNF inhibitors in general is well established across the range of their approved indications, and considered that adalimumab may have a more favourable safety profile compared to infliximab.
- 5.20. The Committee considered that the main advantage of adalimumab over infliximab is subcutaneous administration, and that the relative ease of administration with adalimumab would likely result in it being used as the first-line TNF inhibitor before infliximab, should it be funded for uveitis. The Committee considered that adalimumab

injections would likely be administered in primary care, with most patients (or their caregivers) being able to self-administer at home following appropriate training.

- 5.21. The Committee considered that adalimumab would most benefit those patients with active uveitis that is refractory to corticosteroids and immunomodulatory therapy. The Committee noted that treatment with TNF inhibitors has steroid sparing effects, which may reduce the risks associated with long-term steroid use. The Committee noted the current infliximab hospital restrictions for the treatment of chronic and severe uveitis, and considered that these restrictions are also appropriate for adalimumab and could be applied to both the community and hospital setting. The Committee noted that the current infliximab renewal restriction has objective measures of ongoing response and benefit from treatment, which the Committee considered encourages clinicians to stop treatment if response from treatment is no longer adequate. The Committee considered that approximately 55 to 60 patients per year would be eligible for adalimumab using the current infliximab restrictions.
- 5.22. The Committee considered that if access to adalimumab were widened to include uveitis, it would likely be used as an extra line of TNF therapy, rather than replacing infliximab. The Committee considered that adalimumab would likely delay the eventual use of infliximab for the treatment of uveitis. The Committee noted that this would lead to an increase in TNF expenditure in this market in both the short and long term, due to adalimumab being more accessible to patients in the community and from patients eventually progressing from adalimumab to infliximab. The Committee considered that should adalimumab be used in the community for the treatment of uveitis, this would not change the use of existing immunomodulators, nor encourage earlier use of TNF inhibitors due to existing treatments being oral tablets and capsules which are less invasive than subcutaneous injections.
- 5.23. The Committee considered that the widening of access to adalimumab for uveitis would likely reduce some demand on hospital infusion services in the short term, however this would be met with an increased demand in primary care for the initiation of treatment, monitoring, and administration of adalimumab. The Committee considered that the applicant's estimate for the cost per infusion of infliximab as an offset to be reflective of current practice in New Zealand. The Committee noted that infliximab is administered every 4 to 6 weeks whereas adalimumab is administered every 2 weeks.
- 5.24. The Committee considered that based on the information provided, access to adalimumab should be widened for the treatment of uveitis with a low priority. The Committee considered that whilst there is better quality evidence supporting use of adalimumab for the treatment of uveitis than infliximab, the applicability of that evidence to the New Zealand setting remains uncertain. The Committee noted that trials of infliximab for uveitis were also of low quality.

## **6. Atezolizumab for locally advanced or metastatic non-small cell lung cancer after prior chemotherapy**

### **Application**

- 6.1. The Committee considered an application from Roche (NZ) Limited for the funding of atezolizumab for the second or third-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

### **Recommendation**

- 6.2. The Committee **recommended** that atezolizumab for the second or third-line treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy be funded with low priority.
- 6.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

## Discussion

- 6.4. The Committee noted that lung cancer is the fifth most common cancer registration in 2013, with NSCLC comprising up to 70% of lung cancers in New Zealand, and that the majority of NSCLC patients present with advanced stage III or IV disease at diagnosis.
- 6.5. The Committee noted that survival rates for patients with advanced NSCLC are poor with currently funded treatments; the 1-year survival for patients with stage IV disease treated with chemotherapy is 10%.
- 6.6. The Committee noted that lung cancer registration and mortality rates are consistently higher for Maori when compared with non-Maori.
- 6.7. The Committee noted that atezolizumab is a humanized immunoglobulin monoclonal antibody programmed cell death protein 1 ligand 1 (PD-L1) inhibitor which binds directly to PD-L1 on both tumour infiltrating immune cells or tumour cells thereby preventing the binding to the receptor programmed cell death protein 1 (PD-1) and B7.1 on activated T-lymphocytes and other immune cells.
- 6.8. The Committee noted that PTAC had recently considered applications for two anti-PD-1 immune checkpoint inhibitors, nivolumab and pembrolizumab, in the same patient groups, namely as a second or third-line treatment for NSCLC. The Committee noted PTAC had recommended both be funded with low priority primarily due to immaturity of current data, particularly overall survival, and uncertainty regarding long-term clinically meaningful gains. The Committee noted that PTAC had deferred making a recommendation for pembrolizumab for previously untreated NSCLC patients (first-line) pending publication of mature survival data and further information regarding the potential use of PD-L1 expression as a biomarker.
- 6.9. The Committee noted that atezolizumab and nivolumab were indicated for use in NSCLC irrespective of histology or biomarker, whereas pembrolizumab was indicated for PD-L1 positive NSCLC patients.
- 6.10. The Committee noted that the recommended dose for atezolizumab is a 1200 mg fixed dose administered by intravenous infusion over 30 minutes every 3 weeks.
- 6.11. The Committee noted that the primary evidence for the use of atezolizumab for the treatment of advanced NSCLC is from two randomised clinical trials, the POPLAR (Fehrenbacher et al Lancet 2016;387:1837-46) and OAK (Rittmeyer et al. Lancet 2017;389:255-65) studies.
- 6.12. The Committee noted the POPLAR study is an open-label, phase II randomised controlled trial comparing atezolizumab (1200 mg every 3 weeks, n=142) with docetaxel (75 mg/m<sup>2</sup> every 3 weeks, n=135) in patients with NSCLC who progressed post-platinum chemotherapy.
- 6.13. The Committee noted overall survival (OS) in the intention-to-treat (ITT) population, the primary endpoint, was 12.6 months (95% CI 9.7–16.4) for atezolizumab versus 9.7 months (8.6–12.0) for docetaxel (hazard ratio [HR] 0.73 [95% CI 0.53–0.99]; p=0.04).
- 6.14. The Committee noted the OAK study is a randomised, open-label, phase III trial comparing atezolizumab (1200 mg every 3 weeks, n=425) with docetaxel (75 mg/m<sup>2</sup> every 3 weeks, n=425) in patients with locally advanced or metastatic NSCLC that had progressed during or after treatment with a platinum-containing regimen.
- 6.15. The Committee noted eligibility criteria included squamous or non-squamous NSCLC, age 18 years or older, measurable disease as per RECIST v1.1, ECOG 0-1, prior treatment with 1-2 previous cytotoxic chemotherapy regimens (1 or more platinum-based) for stage IIIb or IV disease. The Committee noted that patients with EGFR mutations or

ALK fusion oncogene were additionally required to have received treatment with a tyrosine kinase inhibitor.

- 6.16. The Committee noted that exclusion criteria included a history of autoimmune disease, or prior treatment with docetaxel, CD137 agonists, anti-CTLA4 or therapies targeting PD-L1 or PD-1 pathways.
- 6.17. The Committee noted that patients were stratified by number of previous chemotherapy regimens, histology, and PD-L1 expression. The Committee noted that PD-L1 expression was divided in five groups based on percentage expression on tumour cells or tumour-infiltrating immune cells as assessed centrally and prospectively in archival or fresh tumour samples using the Ventana SP142 assay.
- 6.18. The Committee noted that treatment was administered until unacceptable toxicity or disease progression as assessed by investigator but that treatment could continue beyond disease progression if the investigator deemed the patient to be receiving clinical benefit.
- 6.19. The Committee noted that no crossover to atezolizumab was permitted, however, 19 patients in the atezolizumab group and 73 patients in the docetaxel group went on to receive subsequent immunotherapy treatment, primarily with nivolumab.
- 6.20. The Committee noted that median treatment duration was 3.4 months (range 0–26) with atezolizumab and 2.1 months (range 0–23) with docetaxel. The Committee noted that 40% of patients receiving atezolizumab were treated beyond progression, with a median treatment duration beyond progression of three cycles (range 1–34).
- 6.21. The Committee noted that at the primary analysis (data cut-off July 7, 2016), the median follow-up was 21 months and that 569 patients had died (27 fewer in the atezolizumab group than the docetaxel group).
- 6.22. In the ITT population, median OS, the primary endpoint, was 13.8 months [95% CI 11.8–15.7] with atezolizumab vs 9.6 months [8.6–11.2] with docetaxel; HR 0.73 [95% CI 0.62–0.87],  $p=0.0003$ , a 4.2 month difference.
- 6.23. The Committee noted that grade 3 or 4 adverse events were reported in 227 (37%) of 609 patients treated with atezolizumab and 310 (54%) of 578 patients treated with docetaxel.
- 6.24. The Committee considered that, when compared to docetaxel, atezolizumab appeared to have an improved adverse event profile, however, considered that longer-term follow up may show an increase in autoimmune toxicity, characteristic of previously discussed immune checkpoint inhibitors. Members considered that the extent of immunological adverse events was uncertain but could be significant.
- 6.25. The Committee considered that the OAK study was well designed in that the primary endpoint was OS, and crossover was not permitted.
- 6.26. The Committee considered the evidence for the use of atezolizumab in previously treated NSCLC patients to be of moderate strength and high quality, although it is largely from only one phase III trial with only short term survival data. The Committee noted that there were a number of ongoing studies for the use of atezolizumab in NSCLC and considered the evidence base would improve within the next 12-24 months.
- 6.27. The Committee considered that due to the immaturity of currently available data, there was a high level of uncertainty regarding the long-term benefit and risks of atezolizumab for NSCLC and the appropriate duration of treatment.
- 6.28. The Committee considered that from the preliminary available data there did not appear to be a long-term survival benefit from treatment with atezolizumab and that it was not

appropriate to extrapolate current data of possible long term survival from immune checkpoint inhibitor trials undertaken in advanced melanoma populations to advanced NSCLC.

- 6.29. The Committee considered that while there appeared to be a correlation between increased PD-L1 expression and increased response rates to immune checkpoint inhibitors in published literature (Herbst et al. *Nature* 2014;515:563-7; Rizvi et al. *Science* 2015; 348:124–8; Abdel-Rahman *Crit Rev Oncol/Hematol.* 2016;101:75–85; Grigg & Rizvi. *J Immunother Cancer.* 2016;4:48), the current evidence did not suggest that higher PD-L1 expression translated to long-term survival or different adverse event profiles.
- 6.30. The Committee considered that benefit over docetaxel was seen in all previously treated NSCLC patients irrespective of PD-L1 expression or histology and that there remained significant uncertainty regarding whether PD-L1 expression could be used to target treatment and that further information was needed.
- 6.31. The Committee considered that there was no evidence, due to the lack of any comparative trials, to suggest that any one immune checkpoint inhibitor provides additional health benefit or harm compared to the others in the treatment of NSCLC. The Committee noted that published reviews consider anti-PD-1 and anti-PD-L1 agents as one class of treatment (Leventakos et al. *BioDrugs* 2016;30:397–405; lafolla & Juergens R. *Front Oncol.* 2017;7:67).
- 6.32. The Committee considered there is class effect for immune checkpoint inhibitors in the treatment of previously-treated advanced NSCLC and that, based on currently available evidence, atezolizumab, nivolumab and pembrolizumab had the same or similar clinical effect in this population.
- 6.33. The Committee noted that if an immune checkpoint inhibitor were to be funded for advanced NSCLC patients this would likely have a significant impact on DHB infusion services.
- 6.34. The Committee considered the application should be referred to the Cancer Treatments Subcommittee for advice particularly regarding appropriate access criteria.

## **7. Cobimetinib plus vemurafenib – unresectable or metastatic melanoma**

### **Application**

- 7.1. The Committee considered an application from Roche Products NZ Ltd for the funding of vemurafenib (Zelboraf) in combination with cobimetinib (Cotellic) for patients with unresectable or metastatic melanoma with BRAF V600 mutation.
- 7.2. The Committee noted that updated advice was also sought from PHARMAC staff regarding the previously considered applications for other BRAF and MEK melanoma treatments - vemurafenib monotherapy, dabrafenib monotherapy, or dabrafenib /trametinib.

### **Recommendation**

- 7.3. The Committee **recommended** that the application for vemurafenib in combination with cobimetinib for patients with unresectable or metastatic melanoma with BRAF V600 mutation be declined.
- 7.4. The Committee reiterated its previous recommendations that the previously considered applications for BRAF inhibitors as monotherapy (vemurafenib, dabrafenib) or in combination with a MEK inhibitor (dabrafenib/trametinib) be declined.

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

## Discussion

- 7.6. The Committee noted that the application from Roche NZ Ltd was for the use of the BRAF inhibitor, vemurafenib in combination with MEK inhibitor, cobimetinib for patients with unresectable or metastatic melanoma with BRAFV600 mutations. The Committee considered that around 25%-50% of advanced melanoma patients in New Zealand would have BRAF mutation positive disease.
- 7.7. The Committee noted that applications for funding of BRAF and MEK targeted treatments – vemurafenib monotherapy, dabrafenib monotherapy and dabrafenib in combination with trametinib – for the treatment of patients with BRAF positive advanced melanoma had been previously considered by PTAC and CaTSOP.
- 7.8. The Committee noted that PD-1 inhibitors, nivolumab and pembrolizumab, for the treatment of advanced melanoma had been funded since 1 July and 1 September 2016 respectively. The Committee noted that BRAF mutation status had no bearing on current access to funded PD-1 inhibitors for advanced melanoma patients.
- 7.9. The Committee noted that at its meeting in September 2016, the Cancer Treatments Subcommittee had highlighted that while the melanoma treatment landscape had changed with the funding of PD-1 inhibitors, there is a potential niche for the use of BRAF/MEK targeted treatments for patients with rapidly progressive BRAF mutant metastatic melanoma as a bridge to PD-1 inhibitor therapy. The Committee noted that current access criteria for PD-1 inhibitors excludes patients with ECOG >2, which includes patients with rapidly progressive disease, and that treatment options for these patients are limited.
- 7.10. The Committee noted that at its November 2016, PTAC noted that no new evidence had been considered by the Subcommittee to support the use of these treatments for rapidly progressive patients and that this represented a different patient population than had previously been considered. The Committee noted that in November 2016, PTAC had reiterated its previous recommendations that funding for BRAF/MEK treatments (vemurafenib monotherapy, dabrafenib monotherapy and dabrafenib in combination with trametinib) be declined. The Committee noted that this recommendation was influenced by uncertainty about the magnitude and duration of benefit, the associated toxicity, the high pricing sought, and the recent funding of PD-1 inhibitors for patients with advanced melanoma.

## Evidence

- 7.11. The Committee noted that the pivotal evidence for the use of vemurafenib in combination with cobimetinib for the treatment of patients with BRAF mutated advanced melanoma is from the CoBRIM study - a randomised, double-blind, placebo-controlled, phase III study of 495 patients with previously untreated, unresectable, locally advanced or metastatic BRAF V600 mutation-positive melanoma (Larkin et al. NEJM 2014;371:1867-76).
- 7.12. The Committee noted that participants were randomly assigned in a 1:1 ratio to receive vemurafenib (960 mg b.d.) together with either placebo (n=248, control group) or cobimetinib at a dose of 60 mg once daily for 21 days followed by 7 days off (n=247, combination group) until patients withdrew consent, unacceptable adverse effects, or disease progression. The Committee noted that continuation of the study treatment or crossover after disease progression was not permitted. The Committee noted that modification of the cobimetinib or vemurafenib dose was allowed for management of adverse events, with guidelines for events of prespecified type and grade.
- 7.13. The Committee noted that eligibility criteria included patients of at least 18 years of age, histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma

with a BRAF V600 mutation detected with the use of a real-time PCR assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems); measurable disease according to the RECIST v1.1 criteria, an ECOG 0-1; and adequate haematologic, hepatic, renal and cardiac function. The Committee noted that no patients with ECOG of 2 or greater were included in the trial. The Committee noted that New Zealand patients were included in the CoBRIM study population.

- 7.14. The Committee noted that exclusion criteria included prior BRAF or MEK inhibitor therapy; current, severe, uncontrolled systemic disease, and active CNS lesions.
- 7.15. The Committee noted that at a median follow up of 7.3 months (range 0.5-16.5) the median progression-free survival (PFS), the primary end point as assessed by investigator, in the combination group was 9.9 months (9.0-NR) vs 6.2 months (5.6-7.4) in the control group (HR for death and disease progression, 0.51; 95% CI 0.39-0.68;  $p < 0.001$ ).
- 7.16. The Committee noted that interim analyses of overall survival (OS) showed 9-month survival rates of 81% in the combination group (95% CI, 75-87) and 73% in the control group (95% CI, 65-80). The Committee noted that at the time of PFS analysis the median OS was not reached in either group.
- 7.17. The Committee noted that there were an increased number of grade 4 adverse events and deaths in the combination group versus the control group, 13% and 2.3% versus 9% and 1.3% respectively. The Committee considered that the adverse event profile of vemurafenib/cobimetinib appeared to be consistent with that reported previously for other targeted BRAF/MEK treatments for advanced melanoma.
- 7.18. The Committee noted that long-term follow-up of the coBRIM study (Ascierto et al. *Lancet Oncol* 2016;17;1248-60), at a median follow-up of 14.2 months (IQR 8.5–17.3), the updated investigator-assessed median PFS was 12.3 months (95% CI 9.5–13.4) for the combination group versus 7.2 months (5.6–7.5) for the control group (HR 0.58 [95% CI 0.46–0.72],  $p < 0.001$ ).
- 7.19. The Committee noted that at the time of the protocol-specified final OS analysis, median follow-up was 18.5 months (IQR 8.5–23.5), median OS was 22.3 months for the combination group (95% CI 20.3-not estimable) and 17.4 months for the control group (95% CI 15.0-19.8) (HR 0.70, 95 CI 0.55-0.90,  $p = 0.005$ ).
- 7.20. The Committee noted that Ascierto et al included patient-reported health-related quality of life as assessed by the European Organisation for Research and Cancer (EORTC) Quality of Life Questionnaire Core 30 at baseline, days 1 and 15 of cycles 1 and 2, and day 1 of every other cycle thereafter (28 day cycles) until patient withdrawal or end of study. However, the Committee noted that quality of life data were only evaluable through to cycle 8 day 1, after which there were less than 25% of patients with baseline quality of life scores who remained enrolled in the combination group, which the authors considered was too few patients to allow meaningful conclusions to be drawn.
- 7.21. The Committee noted that the median duration of treatment for patients in the combination group was 9.0 months with cobimetinib (95% CI 8.1–10.2) and 9.2 months with vemurafenib (8.4–11.0); and the median duration of vemurafenib treatment in the control group was 5.8 months (95% CI 5.5-7.4).
- 7.22. The Committee noted that 37% of patients in the combination group and 42% in the control group went on to receive immunotherapy treatment including subsequent PD-1/PD-L1 monotherapy. The Committee considered that treatment with BRAF/MEK did not appear to reduce your likelihood of progressing to second-line treatment.
- 7.23. Overall, the Committee considered that there was evidence of a moderate effect size for the use of vemurafenib/cobimetinib when compared to best supportive care in advanced

melanoma patients with good performance status. However, the Committee considered that this effect did not appear to be durable with a PFS gain of only 5 months.

- 7.24. The Committee considered that there was no published evidence directly comparing BRAF/MEK inhibitor treatments and current standard of care in a New Zealand context (pembrolizumab and nivolumab).
- 7.25. The Committee considered that the use of BRAF/MEK inhibitors first-line was largely due to the historical introduction of these treatments internationally prior to the advent of immune checkpoint inhibition.
- 7.26. The Committee considered that, given the relatively short time to response with these treatments, their use in a first-line setting may be the most appropriate place in the treatment paradigm. However, the Committee considered that currently published evidence was unresolved regarding the utility of BRAF inhibitor prior to immune checkpoint inhibition. The Committee considered that it appears patients who are sequentially treated with BRAF inhibitors and immune checkpoint inhibitors may have worse outcomes than those who receive immune checkpoint inhibitors only. (Grobe et al. *Lancet Oncol* 2015;16:e522-26; Johnson et al. *J Immunother* 2017;40:31-5; Amin et al. *J Immunother of Cancer* 2016;4:44; Ackeman et al. *Cancer* 2014;1695-1701).
- 7.27. The Committee acknowledged that there remains an unmet health need for patients with advanced melanoma and an ECOG score of >2 (whether BRAF mutation positive or negative), but considered there is currently a lack of evidence to support the use of BRAF/MEK inhibitors in this setting.
- 7.28. The Committee considered that the funding of BRAF/MEK inhibitor treatments should be further considered once evidence to support their use in advanced melanoma patients with ECOG >2 became available.
- 7.29. The Subcommittee considered that based on currently published data the BRAF/MEK combination treatments, dabrafenib/trametinib and vemurafenib/cobimetinib, had the same or similar outcome in the treatment of BRAF mutation positive advanced melanoma.

## 8. Glecaprevir and Pibrentasvir – Chronic Hepatitis C

### Application

- 8.1. The Committee considered the application from AbbVie for Glecaprevir/Pibrentasvir (Maviret) for the treatment of chronic hepatitis C in adults.

### Recommendation

- 8.2. The Committee **recommended** that the application from AbbVie for the funding of Glecaprevir/pibrentasvir for the treatment of chronic hepatitis C in adults be funded with a medium priority, conditional on registration with Medsafe and publication in peer-reviewed medical journals.
- 8.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### Discussion

- 8.4. The Committee noted that Viekira Pak ± ribavirin has been funded without restriction for the treatment of hepatitis C virus (HCV) genotype 1 and noted that ledipasvir with sofosbuvir (Harvoni) has been funded for the treatment of patients with hepatitis C with advanced disease since July 2016. Access to Harvoni has been widened since 12 June 2017 to include patients with a lower end-stage liver disease (MELD) score of 12 or greater.

- 8.5. Members noted that the application for funding of glecaprevir/pibrentasvir was for the treatment of chronic hepatitis C infection in adults, including genotypes 1 to 6, without restriction. The Committee noted that the supplier proposed that Glecaprevir/pibrentasvir replace Viekira Pak ± ribavirin.
- 8.6. The Committee noted that glecaprevir/pibrentasvir is a combination of NS3/4 protease inhibitor and NS5A inhibitor. Three tablets are to be taken once daily. Members noted that the treatment duration was 8 weeks for treatment naïve patients, and for treatment-experienced patients with genotype 1, 2, 4, 5 and 6 hepatitis C infection.
- 8.7. Treatment experienced patients infected with genotype 3 require 16 weeks of treatment, as do patients with genotype 1, 2, 4, 5, and 6 that have previously received treatment with NS5A inhibitors. Members noted that 12 weeks of treatment is recommended for patients with cirrhosis. Members noted that ribavirin is not required, and also noted that it glecaprevir/pibrentasvir not indicated for patients with decompensated liver disease.
- 8.8. Members considered that treatment-naïve, non-cirrhotic patients would make up 90% of patients in New Zealand.
- 8.9. The Committee noted that glecaprevir/pibrentasvir was evaluated in nine Phase II and Phase III clinical trials, that included more than 2,800 patients. Members reviewed unpublished clinical trial data provided by the supplier. The Committee recommended that study results be published in a peer-reviewed medical journal before a funding decision is made. PHARMAC staff note that some of these clinical trials have since been published in numerous peer reviewed journals (Poordad, et al., *Hepatology*. 2017; 66:389-97; Kwo, et al., *J Hepatol*. 67:263-71; Forns et al., *Lancet Infect Dis*. 2017. doi: 10.1016/S1473-3099(17)30496-6).
- 8.10. Members reviewed the safety and efficacy results of the ENDURANCE, EXPEDITION, SURVEYOR and MAGELLAN trials, as reported in the unpublished clinical trial data in the manuscript supplied by the applicant.
- 8.11. The Committee reviewed the unpublished results of the ENDURANCE-1 trial, which compared glecaprevir/pibrentasvir treatment for 12 weeks against 8 weeks in a randomised, open-label trial of HCV genotype 1 that were either treatment naïve or treatment experienced. Members noted that for patients receiving 8 weeks of treatment, 99.1% achieved SVR12, compared to 99.7% of patients that achieved SVR12 following 12 weeks of treatment.
- 8.12. Members reviewed the unpublished results of the ENDURANCE-2 trial, which compared 12 weeks of glecaprevir/pibrentasvir treatment against placebo in a randomised, double blind, trial of HCV genotype 2 infected patients that were either treatment naïve or treatment experienced. Members noted that 99.5% of patients achieved SVR12, and 1.5 percent of patients treated with glecaprevir/pibrentasvir were reported as having a serious adverse event (SAE), with none discontinuing because of a SAE.
- 8.13. Members reviewed the unpublished results of the ENDURANCE 3 trial, which evaluated the efficacy of glecaprevir/pibrentasvir compared to sofosbuvir with daclatasvir for treatment-naïve patients with HCV genotype 3. Treatment with glecaprevir/pibrentasvir for 8 weeks resulted in 95.3% of patients achieving SVR12 compared to treatment with sofosbuvir with daclatasvir which resulted in 95% of patients achieving SVR12; Members noted that 2.1% of glecaprevir/pibrentasvir treated patients were reported as having a “serious adverse event” (SAE)
- 8.14. The Committee reviewed the unpublished results of the SURVEYOR 1 and 2 trials and noted that the SURVEYOR 2 trial assessed the efficacy of glecaprevir/pibrentasvir for 8, 12 or 16 weeks in patients with or without compensated cirrhosis, including genotype 3 infected patients that were either treatment naïve or treatment experienced. Members noted that for treatment naïve genotype 3 infected patients, the SVR12 was 97% for non-

cirrhotic patients, 100% for cirrhotic patients, and for treatment experienced, the SVR12 was 92% for non-cirrhotic, and 75% for cirrhotic patients. Members noted that there were small numbers of treatment experienced cirrhotic patients therefore an accurate assessment of efficacy in this difficult to treat group was not achieved. There was no discontinuation of study participants due to adverse events.

- 8.15. Members also evaluated the efficacy of glecaprevir/pibrentasvir for 12 or 16 weeks for the treatment of patients previously failed by DAA treatment in the MAGELLAN-1 study (unpublished data), which revealed that there may be a possible added benefit to a longer treatment duration, but no added benefit to including ribavirin. The Committee noted that the efficacy of glecaprevir/pibrentasvir ranged from SVR12 of 79% to 100% depending on previous treatment history and genotype.
- 8.16. Members compared glecaprevir/pibrentasvir to sofosbuvir and velpatasvir (Epcalsa) for the treatment of chronic hepatitis C and noted that glecaprevir/pibrentasvir requires a shorter treatment duration of 8 weeks, compared to treatment with Eplusa, which is 12 weeks. Members also noted that both treatments are taken once daily, but that glecaprevir/pibrentasvir is formulated in three separate tablets, compared to Eplusa, which is a single tablet. Members considered that there were suitability advantages to each. Members considered that the efficacy and safety of both pangenotypic treatments was excellent and there were no important differences in these parameters between the two drugs, noting that neither were affected by NS5A (resistance-associated variants) RAVS. The Committee noted that glecaprevir/pibrentasvir is contra-indicated in decompensated cirrhosis (Childs-Pugh B and C). It was noted that the numbers of these patients in New Zealand is relatively small and decreasing, but that treatment, such as Harvoni, would still be required.
- 8.17. In comparison with Viekira Pak for the treatment of genotype 1 HCV, Members noted that glecaprevir/pibrentasvir has better efficacy, no requirement for ribavirin, which reduces the number of side-effects and complexity of treatment, significantly less drug-drug interactions and has a reduced treatment duration. The Committee considered that these benefits, along with no requirement for pre-treatment genotype testing, should make prescribing by general practitioners straight forward (unpublished data from ENDURANCE-3 trial supports the recommendation for only 8 weeks' treatment for genotype 3, which is the most difficult to treat genotype). Members noted that there would still be a requirement for pre-testing with a Fibroscan to detect cirrhosis, which needs to be easily available for use by general practitioners.
- 8.18. Members noted identifying and targeting treatment to the difficult to reach HCV infected populations posed a challenge to reducing the transmission of hepatitis C. The Committee considered that the easier treatment regime of glecaprevir/pibrentasvir compared to Viekira Pak would be beneficial to successful treatment in primary care. Members noted that there are additional barriers to the eradication of hepatitis C in New Zealand other than providing effective treatments.
- 8.19. The Committee noted that while the efficacy of SVR12 indicated excellent efficacy in the ability of pangenotypic DAAs to clear HCV, long-term follow up data demonstrating clinical outcomes, in particular the effect of pangenotypic DAAs on rates of hepatocellular carcinoma, requirement for liver transplant and morbidity and mortality, is not yet known. Members note they look forward to reviewing this data when it becomes available.

## **9. Sofosbuvir/Velpatasvir – Chronic Hepatitis C**

### **Application**

- 9.1. The Committee considered the application from Gilead for Sofosbuvir with velpatasvir (Eplusa) for the treatment of chronic hepatitis C in adults.

### **Recommendation**

- 9.2. The Committee **recommended** that the application from Gilead for the funding of sofosbuvir with velpatasvir for the treatment of chronic hepatitis C in adults be funded with a medium priority.
- 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 Viekira Pak ± ribavirin has been funded without restriction for the treatment of hepatitis C virus (HCV) genotype 1 and noted that ledipasvir with sofosbuvir (Harvoni), has been funded for the treatment of patients with hepatitis C with advanced disease since July 2016. Access to Harvoni has been widened since 12 June 2017 to include patients with a lower end-stage liver disease (MELD) score of 12 or greater.
- 9.5. Members noted that the application for funding of sofosbuvir with velpatasvir is for the treatment of chronic hepatitis C infection in patients over the age of 18, including genotypes 1 to 6. The Committee noted that the requested restriction would mean that sofosbuvir with velpatasvir would be funded for patients who are currently eligible for Viekira Pak or Harvoni.
- 9.6. The Committee noted that sofosbuvir with velpatasvir is a combination NS5B and NS5A inhibitor, and is supplied as a combination tablet to be taken once daily. Members noted that the treatment duration is 12 weeks, regardless of HCV genotype, prior treatment status or cirrhotic status. Members noted that sofosbuvir with velpatasvir + ribavirin is indicated for patients with decompensated cirrhosis.
- 9.7. Members considered that treatment-naïve, non-cirrhotic patients would make up 90-95% of patients in New Zealand.
- 9.8. The Committee noted that sofosbuvir with velpatasvir was evaluated in five clinical trials (the ASTRAL studies). Members reviewed the safety and efficacy results of the ASTRAL trials, and noted that the primary endpoint in all studies was a sustained virologic response 12 weeks after treatment (SVR12).
- 9.9. The Committee reviewed the results of ASTRAL-1 trial (Feld et al. NEJM, 2015;373:2599-607), which compared sofosbuvir with velpatasvir treatment against placebo for 12 weeks in a randomised trial of patients infected with HCV genotype 1,2,4,5 or 6 that were either treatment naïve or treatment experienced. Members noted that that the SVR12 was 99% in genotype 1 and 100% in genotype 2. Serious adverse events were reported in 2% of patients in the treatment arm, and rates of adverse events were similar in the treatment and placebo arms.
- 9.10. Members reviewed the results of the ASTRAL-2 and ASTRAL-3 trials (Foster et al. NEJM, 2015;373:2608-17), which compared 12 weeks of sofosbuvir with velpatasvir treatment to 12 weeks of treatment with sofosbuvir and ribavirin for genotype 2 or genotype 3 HCV infected patients, respectively. The Committee noted that 99% of sofosbuvir with velpatasvir treated genotype 2 patients achieved SVR12 compared to 94% of patients treated with sofosbuvir and ribavirin. Members noted that for 95% of genotype 3 patients achieved SVR12 compared to 80% of patients treated with sofosbuvir with ribavirin. Members noted that rates of serious adverse events were low in both arms.
- 9.11. Members reviewed the results of the ASTRAL-4 trial (Curry et al. NEJM. 2015;373:2618-28), which evaluated the efficacy of sofosbuvir with velpatasvir treatment for 12 or 24 weeks compared to 12 weeks of sofosbuvir with velpatasvir with ribavirin in patients with decompensated cirrhosis. The Committee noted that the median MELD score of patients was 10, and post-liver transplant patients were excluded. Members noted that SVR at 12 weeks of treatment with sofosbuvir with velpatasvir was 83%, 24 weeks was 86% and sofosbuvir with velpatasvir combined with ribavirin for 12 weeks had an SVR rate of 94%.

Members noted that 18% of patients reported adverse events, and 9 participants discontinued treatment due to adverse events.

- 9.12. The Committee reviewed the results of the ASTRAL-5 study (Wyles et al. Clin Infect Dis. 2017; doi: 10.1093/cid/cix260), which was a small prospective cohort study (n=104) of HCV and HIV1 co-infected patients. Members noted that participants were not restricted by genotype, but over 70% had genotype 1 HCV infection, 18% of patients had cirrhosis and 29% of patients were treatment-experiences. Members noted that following 12 weeks of treatment with sofosbuvir and velpatasvir, the overall SVR12 was 95%, with 1.9% of patients reported to have severe adverse events, and 1.9 percent of patient discontinuing treatment due to adverse events. The Committee noted that the SVR rates achieved in the presence of HIV co-infection were consistent with the SVR12 efficacy rates in the subgroups studied in the other ASTRAL trials.
- 9.13. Members noted that the strength of the evidence for SVR12 was excellent, but noted a limitation in the quality of evidence because no quality of life data was reported in any of the ASTRAL studies. The Committee also noted that there was no direct comparison with Harvoni, which is currently funded by PHARMAC.
- 9.14. Members compared another pangenotypic treatment, glecaprevir/pibrentasvir (Maviret) to sofosbuvir and velpatasvir for the treatment of chronic hepatitis C and noted that glecaprevir/pibrentasvir requires a shorter treatment duration of 8 weeks, compared to treatment with sofosbuvir with velpatasvir, which is 12 weeks. Members also noted that both treatments are taken once daily, but that glecaprevir/pibrentasvir is formulated in three separate tablets, compared to sofosbuvir with velpatasvir, which is a single tablet. Members considered that there were suitability advantages to each. Members considered that the efficacy and safety of both pangenotypic treatments was excellent and there were no important differences in these parameters between the two drugs, noting that both were also not affected by NS5A (resistance-associated variants) RASVs. The Committee noted that glecaprevir/pibrentasvir is contra-indicated in decompensated cirrhosis (Childs-Pugh B and C), while sofosbuvir with velpatasvir can be used in combination with ribavirin to treat this patient group. It was noted that the numbers of these patients in New Zealand is relatively small and decreasing, but a treatment for these patients, such as Harvoni, would still be required.
- 9.15. In comparison with Viekira Pak for the treatment of genotype 1 HCV, Members noted that sofosbuvir with velpatasvir has better efficacy, no requirement for ribavirin for most patients, which reduces the number of side-effects and complexity of treatment, no drug-drug interactions and has a reduced number of tablets to be taken daily. The Committee considered that these benefits, along with no requirement for pre-treatment genotype testing, should make prescribing by general practitioners straight-forward. Members noted that there would still be a requirement for pre-testing with a Fibroscan to detect cirrhosis, which needs to be easily available for use by general practitioners.
- 9.16. Members noted identifying and targeting treatment to the difficult to reach HCV infected populations posed a challenge to reducing the transmission of hepatitis C. The Committee considered that the straight forward treatment regime of sofosbuvir with velpatasvir compared to Viekira Pak would be beneficial to successful treatment in primary care and considered that one treatment for all patients (including decompensated patients) would further simplify hepatitis C treatment. Members noted that there are additional barriers to the eradication of hepatitis C in New Zealand other than providing effective treatments.
- 9.17. The Committee noted that while the efficacy of SVR12 indicated excellent efficacy in the ability of pangenotypic DAAs to clear HCV, long-term follow up data demonstrating clinical outcomes, in particular the effect of pangenotypic DAAs on rates of hepatocellular carcinoma, requirement for liver transplant and morbidity and mortality, is not yet known. Members note they look forward to reviewing this data when it becomes available.

## 10. Peginterferon beta – 1a (rch) – Relapsing forms of multiple sclerosis

### Application

- 10.1. The Committee considered an application from Biogen for the funding of peginterferon beta-1a fortnightly injection (Plegridy) for the treatment of relapsing remitting multiple sclerosis (RRMS)

### Recommendation

- 10.2. The Committee **recommended** that peginterferon beta-1a fortnightly injection be funded, subject to the same Special Authority criteria for interferon beta 1-a weekly injection, only if cost-neutral to treatment based on interferon beta1-a weekly injection (taking into account likely future price reductions associated with biosimilars of the once weekly formulation, as per PHARMAC's Prescription for Pharmacoeconomic Analysis).
- 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 interferon beta-1a injection is currently funded for patients who meet the Special Authority criteria for the Multiple Sclerosis (MS) treatments and who cannot take fingolimod or natalizumab for clinical reasons.
- 10.5. The Committee noted that the MS treatments had undergone extensive review by both PTAC and the Neurological Subcommittee and that it had previously considered (in February 2014) that the 'newer' MS treatments (fingolimod, natalizumab) appear to have greater efficacy than the 'older MS treatments' (interferon beta-1a, interferon beta-1b and glatiramer acetate) and are most likely more effective at preventing progression of disease if used at earlier stages of disease.
- 10.6. The Committee noted that peginterferon beta-1a is a pegylated formulation of the currently funded interferon beta-1a, administered fortnightly by subcutaneous injection.
- 10.7. The Committee noted that the supplier was seeking funding of peginterferon beta-1a subject to the same Special Authority criteria for interferon beta-1a.
- 10.8. The Committee considered the evidence provided by the supplier in support of its application. The Committee noted that there were no direct head-to-head trials provided comparing peginterferon beta-1a with interferon beta-1a. With regards to the efficacy and safety of peginterferon beta-1a, the Committee considered the most relevant clinical trials provided to be a phase III trial comparing peginterferon beta-1a to placebo (described below) and, in addition, a network meta-analysis comparing treatments indirectly (also detailed below).
- 10.9. ADVANCE (Calabresi et al. Lancet Neurol 2014;14:657-65) was a multicentre, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of peginterferon beta-1a in patients with relapsing MS. Patients were randomly assigned into 3 groups, to receive subcutaneous injections, for 48 weeks, of either placebo or peginterferon beta-1a 125 micrograms two- or four-weekly. The primary outcome was annualised relapse rate (ARR) at 48 weeks. Secondary outcomes included proportion of patients relapsed, disability progression and MRI outcomes.
- 10.10. The Committee noted that the authors reported that the ARR was significantly lower with peginterferon beta-1a every two weeks compared to placebo (ARR 0.256 versus 0.397), thus reducing relapses by approximately one third ((rate ratio two-weekly peginterferon beta-1a versus placebo of 0.644 (95% CI 0.500-0.831; p=0.0007)). With regards to the secondary outcome, sustained disability progression at 48 weeks, the Committee noted that the authors reported the proportion of patients with this at 48 weeks was significantly

- lower with peginterferon beta-1a every 2 weeks compared to placebo ((0.068 versus 0.105, hazard ratio 0.62 (95% CI 0.40 to 0.97, p=0.0383)). The Committee noted the authors reported the most common adverse events associated with peginterferon beta-1a were injection site reactions, influenza-like symptoms, pyrexia, and headache.
- 10.11. Tolley et al. (PLoS ONE 2015;10(6):e0127960) conducted a network meta-analysis indirectly assessing the relative efficacy, safety and tolerability of pegylated interferon versus other injectable relapsing remitting multiple sclerosis (RRMS) treatments. Included studies were randomised controlled trials evaluating > 1 first-line treatments including interferon beta-1a 30, 44, and 22 mcg, interferon beta-1b, and glatiramer acetate in patients with relapsing remitting MS (RRMS).
  - 10.12. The Committee considered, based on the reported results of the meta-analysis, that peginterferon beta-1a every 2 weeks was associated with a statistically significant improvement in ARR when compared to placebo and a numerical improvement compared to all interferons, although none of the comparisons with active comparators were statistically significant. The Committee noted the lesser quality of evidence with such cohort studies (network analyses being indirect comparisons).
  - 10.13. The Committee noted that injection-site reactions were the most frequently reported AE for peginterferon beta-1a, and these annualised risks were similar to those of interferon beta-1a three times weekly and higher than those reported for the interferon beta-1a 30 mcg weekly and the other interferons and glatiramer acetate. The Committee noted that the interferon beta-1a once weekly formulation was reported to have had the lowest reported annualised risk of injection site reactions of all the injectable treatments.
  - 10.14. Overall the Committee considered that the two studies (Calabresi et al., Tolley et al.) suggested that pegylated interferon every two weeks may have similar efficacy to other injectable RRMS treatments (interferon beta-1a, interferon beta-1b and glatiramer acetate) with regard to ARR and disability progression, although being indirect rendered less confidence. With regards to safety, the Committee considered that peginterferon was likely to be similar to that of interferon beta-1a. Members considered that the reported higher annualised risk of injection site reactions from the pegylated formulation (compared with the once weekly formulation) could be due to the route of administration being subcutaneous as opposed to intramuscular.
  - 10.15. Members noted that the estimates of disability progression for the 'older treatments' (interferon beta-1a, interferon beta-1b and glatiramer acetate), used in PHARMAC's health economic model, were in line with recently published evidence from the UK MS Treatments Risk Sharing Scheme (Palace et al. Lancet Neurol 2015;14:497-505).
  - 10.16. The Committee considered that there was insufficient evidence to support the supplier's claim that reduced dosing frequency would benefit adherence, subsequent health outcomes and quality of life. The Committee considered that there was no direct evidence provided to support improved patient adherence, and therefore health benefits, from the fortnightly injection compared to the weekly formulation.
  - 10.17. The Committee considered one non-experimental study regarding injection site reactions and adherence (Beer et al. BMC Neurol. 2011;11:144) and two studies reporting patient preference for injectable disease-modifying MS treatments using discrete choice experiments (DCE) (Poulos et al. Patient 2016;9:171-180; Poulos et al. Ther Adv Neurol Disord. 2016;9:95-104). Overall, the Committee considered that, from this study, the once weekly interferon-beta 1a was reported to be better tolerated than other injectable comparators (fewer injection site reactions and less likely to switch therapies). The two DCE studies reported that there was a preference for a change in injection frequency from daily to fortnightly. The Committee considered that evidence to support a preference for fortnightly as opposed to weekly injections was, however, not consistent between the two DCE studies.

- 10.18. The Committee considered that if peginterferon beta-1a was listed that it would be unlikely to displace treatments other than interferon beta-1a.
- 10.19. The Committee considered that peginterferon beta-1a would be unlikely to produce a health benefit for family, whanau or wider society, that was additional to the health benefits for people with RRMS who have been taking interferon beta-1a.
- 10.20. The Committee considered that patients with RRMS have a high health need; however, this patient group would have the same remaining health needs regardless of whether taking peginterferon beta-1a or interferon beta-1a.
- 10.21. The Committee considered that if peginterferon beta-1a was listed that the majority of patients taking interferon beta-1a would switch to this formulation.
- 10.22. The Committee considered that it was unlikely that there would be any additional costs or savings to the health system that would be attributed to the peginterferon beta-1a formulation, compared with the currently funded formulation.
- 10.23. The Committee noted that the patent on the fortnightly formulation was not due to expire until Jan 2023 and considered that, should there be biosimilar entry of the weekly formulation, this could mean that the proposed price of peginterferon beta-1a at this current time would therefore not continue to be cost-neutral in the future.
- 10.24. Overall the Committee considered that peginterferon beta-1a should be funded only if cost-neutral to treatment based on interferon beta-1a weekly injection (taking into account likely future price reductions, associated with biosimilars, of the once weekly formulation, according to the requirements specified in PHARMAC's Prescription for Pharmacoeconomic Analysis), noting the evidence provided suggesting similar health benefits and risks to the person compared to the currently funded interferon beta-1a weekly formulation.

• **14. Tiotropium bromide – severe asthma (resubmission)**

**Application**

14.1 The Committee considered a resubmission from Boehringer Ingelheim for widened access to the soft mist form of tiotropium (Spiriva Respimat) for the treatment of severe asthma in adults who have experienced at least one exacerbation in the previous 12 months while receiving asthma therapy with at least an inhaled corticosteroid (ICS) and a long acting beta2-agonist (LABA).

**Recommendation**

14.2 The Committee **recommended** the application be declined.

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

**Discussion**

14.4 The Committee noted that it considered an application from Boehringer Ingelheim for the use of the soft mist form of tiotropium (Respimat) for the treatment of severe asthma in adults who meet restriction criteria at its meeting in November 2016 and that it had recommended that the application be declined. The Committee noted that it had previously been unsupportive due to what it considered to be potential safety risks with Respimat being used in a diverse population of COPD patients with many therapeutic options, balanced against the limited evidence of clinical benefits reported by the clinical trials for asthma.

14.5 The Committee noted that at its February 2017 meeting it reviewed correspondence received from Boehringer in January 2017 that sought to withhold from publication the entirety of the tiotropium minutes from the November 2016 PTAC meeting as well as additional evidence provided by Boehringer supporting the safety of tiotropium. The Committee noted that at this meeting (February 2017) it had considered that the recommendation to decline the submission was based more on uncertainty around the clinical benefit of tiotropium bromide when used in patients with severe asthma, rather than specifically related to the safety of tiotropium bromide. The Committee noted that at this meeting (February 2017) it had also considered that in the absence of new evidence (other than an editorial by Jenkins, *N Engl J Med* 2013; 369:1555-6) that no amendment or redaction to the minute was necessary.

14.6 The Committee noted that the information provided for reconsideration at this meeting (May 2017) was a resubmission of the November 2016 application. The Committee considered that this resubmission was largely the same as what was previously reviewed by PTAC in November 2016 and that the key clinical trials supporting the efficacy of tiotropium when used in the proposed population of adults with severe asthma remain unchanged. The Committee noted the resubmission included the following evidence not previously considered around the safety of tiotropium in asthma and COPD:

- Ducharme et al. *Cochrane Database Syst Rev* 2010 Apr 14;(4)
- Bateman et al. *J Allergy Clin Immunol* 2015; 136(4):914-22
- Dahl et al. *Respiratory Medicine* 2016;118: 102-11
- Halpin et al. *International Journal of COPD* 2015;10:239-59

14.7 The Committee noted that at its November 2016 meeting it had reviewed and discussed the following papers regarding efficacy of treatment: Kerstjens et al (*N Engl J Med* 2012;367:1198-207), Ohta et al (*Respirology* 2014;19(supp3):65), Kew et al (*Cochrane*

Database of Systematic Reviews, 2016 issue 1.Art.No:CD011721), Price et al (Asthma Allergy 2015;8:1-13), NICE 2014 recommendation for tiotropium, GINA (2016) guidelines, and the following papers around the safety of tiotropium in asthma: Wise et al (N Engl J Med 2013;369:1491-501), Singh et al (BMJ 2011;342:d3215), Chong et al (Cochrane Database Syst Rev 2012 Sept 12), and Dong et al (Thorax 2013;68:48-56). The Committee considered that it stood by its previous view of the evidence, that whilst an improvement in FEV1 was shown when tiotropium was added to an ICS/LABA in the treatment of patients with severe asthma, the change in FEV1 was substantially less than what had been shown to be the minimal patient perceived difference, that improvements in the patient outcome Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores did not achieve minimal clinically important differences, and that the confidence interval for the change in the frequency and number of exacerbations do not rule out no effect.

- 14.8 The Committee reviewed Ducharme et al 2010 (Cochrane Database Syst Rev 2010 Apr 14;(4)), a systematic review and meta-analysis of randomised control trials where inhaled long acting beta agonists (LABAs) were added to ICS in adults and children over 2 years of age with asthma. The authors found 77 studies which met the meta-analysis' eligibility criteria measuring 21,248 trial participants in total. The study participants were noted to be generally symptomatic at baseline with moderate airway obstruction despite their current ICS regimen. The Committee noted that the addition of a LABA to an ICS lead to a modest improvement in FEV1 of 110 mL (95% CI: 90 mL to 130 mL), however noted that the authors did not comment on whether this increase in FEV1 was considered clinically significant or meaningful.
- 14.9 The Committee reviewed the results of Bateman et al (J Allergy Clin Immunol 2015; 136(4):914-22), a systematic review and network meta-analysis indirect comparison that examined the magnitude of response in randomised, double blinded clinical trials of commonly used asthma drugs when measured with the ACQ-7 and/or AQLQ instruments and whether the treatments exceeded the minimally important difference (MID) as measured using those tools. The authors identified 64 randomised controlled trials for inclusion into this meta-analysis, of which 54 trials used the AQLQ and 11 used the ACQ instrument (1 trial using both). The Committee noted that when compared with placebo, only an ICS with or without a LABA achieved the minimally important difference using either the AQLQ or ACQ or both. The Committee noted the authors' view that future studies should employ methods that reduce the placebo effect seen in patients receiving an ICS as background treatment, and that for most treatments, particularly when asthma therapies are combined, the mean difference between treatment groups exceeding the MID is probably not achievable. The Committee noted that only 11 papers out of 64 included in this study used the ACQ, being the quality of life instrument that was used in Kerstjens 2012, and considered that the results of this paper (Bateman et al 2015) may not be generally applicable to ACQ.
- 14.10 The Committee noted Boehringer's comments about the Santanello et al 1999 (Eur Respir J; 14:23-7), a trial which PTAC had referenced at its November 2016 meeting, describing the relationship between the minimally perceived patient improvement and changes to FEV1. The Committee further noted the comments that patients in the Santanello trial had different baseline characteristics to patients that tiotropium is intended to treat. The Committee however considered that, from the literature available, there is no evidence to suggest that a smaller improvement in FEV1 than what was observed in the Santanello trial, albeit in more heavily treated patients, would influence the patient's perception of benefit.
- 14.11 The Committee considered that the new information provided by Boehringer in the resubmission did not change PTAC's previous view that the evidence for the clinical benefit with add-on tiotropium is limited and uncertain.
- 14.12 In terms of safety, the Committee reviewed Dahl et al 2016 (Resp Med;118:102-11) and Halpin et al, 2015 (Int J COPD;10:239-59), which pooled safety data from tiotropium

asthma and COPD trials respectively, to evaluate the safety and tolerability of tiotropium solution for inhalation delivered via the Respimat device.

- 14.13 The Committee noted that Dahl et al 2016 (*Resp Med* 2016;118:102-11) used pooled safety data from seven phase II and phase III, randomised, double blind, parallel group trials, which investigated once-daily tiotropium Respimat (5 mcg or 2.5 mcg) versus placebo as add-on treatment to different levels of background maintenance therapy, including at least ICS. The exclusion criteria were similar across all seven trials with regards to respiratory and cardiac co-morbidities. The Committee noted that the proportions of patients with adverse events (AEs) were comparable between treatment groups: tiotropium 5 mcg at 60.8%, placebo 5 mcg pool at 62.5%, tiotropium 2.5 mcg at 57.1%, placebo 2.5 mcg pool at 55.1% and that the proportions of cardiac AEs were comparable between tiotropium and placebo: tiotropium 5 mcg at 1.4%, placebo 5 mcg pool at 1.4%, tiotropium 2.5 mcg at 1.4%, placebo 2.5 mcg pool at 1.15%. The most common cardiac AEs were palpitations and tachycardia, none of which were reported in more than 0.5% of patients in any treatment arm. The Committee noted that the proportions of patients with serious AEs were balanced across groups: tiotropium 5 mcg at 4.0%, placebo 5 mcg pool at 4.9%, tiotropium 2.5 mcg at 2.0%, placebo 2.5 mcg pool at 3.3%. The Committee noted that the most frequent AEs reported were asthma, decreased peak expiratory flow rate and nasopharyngitis.
- 14.14 The Committee noted Halpin et al 2015 (*Int J COPD*;10:239-59), a pooled safety analysis from 35 randomised, double blind, parallel group, placebo controlled, clinical trials in patients with COPD (28 HandiHaler, and 7 Respimat), which studied adverse event rates for tiotropium dry powder for inhalation (HandiHaler) and tiotropium solution for inhalation (Respimat). The Committee noted that the included trials used similar inclusion and exclusion criteria. The Committee noted that with regards to cardiac comorbidities in the exclusion criteria, earlier trial protocols had heart failure resulting in hospitalisation in the previous 3 years, cardiac arrhythmia requiring drug treatment, or myocardial infarction (MI) within the past year as exclusion criteria. Other than these specific criteria, heart failure and ischemic heart disease were not excluded. The Committee noted that more recent trials used less stringent exclusion criteria, such as life-threatening cardiac arrhythmia or arrhythmia requiring a change in medication within the last year, heart failure resulting in hospitalisation in the past year, and/or MI within the preceding 6 months.
- 14.15 The Committee noted that safety data from a total of 11,626 placebo patients and 12,929 tiotropium treated patients were analysed by the authors. The Committee noted that the risk of AEs and serious AEs were significantly lower in the pooled tiotropium group (62.6% and 21.7% respectively) compared with the placebo group (65.5% and 22.8% respectively), and there was also a lower risk of fatal AEs in the combined tiotropium group (4.0%) versus placebo (4.5%). The Committee noted that the authors reported no evidence of statistically significant increased risks in major adverse cardiovascular events (MACE; 0.87 RR, 95% CI 0.75–1.01) and fatal MACE (0.90 RR, 95% CI 0.74–1.10) in the combined tiotropium group versus the placebo groups. The Committee however noted that Table 3 of the paper reported patients with cardiac disorders and cardiac arrhythmias, when treated with tiotropium Respimat, experienced higher risks of fatal AEs (3.3% and 4.9% respectively) compared with placebo Respimat (2.0% and 1.4% respectively), and that the difference was statistically significant in cardiac arrhythmia patients. The Committee noted that this increased risk was only observed in those patients being treated with tiotropium Respimat.
- 14.16 The Committee noted the safety data from Karner et al 2014 (*Cochrane Database of Systematic Reviews*), a systematic review and meta-analysis of randomised controlled trials comparing tiotropium to placebo when used for the treatment of COPD. The Committee noted that the authors reported that patients taking tiotropium soft mist inhalers had significantly increased mortality risk compared to placebo (Peto OR 1.47; 95% CI 1.04 to 2.08), whereas fewer patients on tiotropium using the dry powder inhaler died than patients on no treatment.

- 14.17 The Committee considered that there may be a proportion of patients for whom the use of tiotropium Respimat may increase their risk of fatal adverse events, and requested PHARMAC staff write to alert Medsafe and to ask Medsafe to consider amending the datasheet for tiotropium to list the cardiac exclusion criteria used in the above trials (heart failure resulting in hospitalisation in the previous 3 years, cardiac arrhythmia requiring drug treatment, or myocardial infarction (MI) within the past year) and to specify cardiac arrhythmias as a contraindications to tiotropium.
- 14.18 The Committee noted the current New Zealand Adult Asthma Guidelines (Beasley et al. NZMJ 2016) do not recommend tiotropium as an add-on treatment for severe asthma. The Committee considered that single inhaler maintenance and reliever therapy (SMART) should be the treatment against which add-on tiotropium should be compared with, and that the evidence provided does not show improved patient outcomes with add-on tiotropium. The Committee considered that patients with asthma in New Zealand currently have a range of treatment options available and that improved prescribing, health literacy, and adherence to currently available medicines would significantly improve asthma patient outcomes. The Committee considered that the evidence provided in the resubmission did not sufficiently address the uncertainties of clinical benefit and if anything raised more concerns around the safety of tiotropium in COPD.
- 14.19 The Committee considered that its previous recommendation to decline stands.

1. 13. Anti-VEGF

2. Anti-VEGF for 2nd line wAMD

Application

13.1 The Committee reviewed submissions relating to a proposal to fund ranibizumab second line and aflibercept third line for the use in the treatment of neovascular (wet) aged-related macular degeneration.

Recommendation

13.2 The Committee **recommended** that aflibercept be funded as second line anti-VEGF treatment for wAMD after bevacizumab, with a **medium** priority.

13.3 The Committee **recommended** that the funding of a third line anti-VEGF agent for wAMD be **declined**.

13.4 The Committee **recommended** that the proposed access criteria for second line aflibercept be referred to the Ophthalmology Subcommittee for further development, including objective entry and exit criteria.

Discussion

13.5 The Committee noted that in October 2014, the Ophthalmology Subcommittee reviewed aflibercept for the treatment neovascular (wet) age-related macular degeneration (wAMD) and recommended that aflibercept be funded on the HML with a high priority for the second line treatment of wAMD after bevacizumab. The Committee noted that in February 2015 and August 2015 PTAC had recommended that PHARMAC run a Request for Proposal (RFP) process for a second and third line anti-VEGF agent for wAMD.

13.6 The Committee noted that in October 2014, the Ophthalmology Subcommittee had also recommended that ranibizumab should be funded as the third line anti-VEGF agent for patients who are of child bearing age or who have had a myocardial infarction (MI) or a stroke within the last three months. The Committee noted that the Subcommittee considered the risk of systemic exposure with ranibizumab to be less than with either bevacizumab or aflibercept.

13.7 The Committee noted that in February 2015, PTAC had considered that whilst the Ophthalmology Subcommittee were supportive of aflibercept based in part on clinical opinions that aflibercept may be superior to ranibizumab, there was no evidence available to demonstrate superiority of aflibercept over ranibizumab in wAMD. The Committee noted that in February 2015, PTAC considered that there was no clinical reason not to run a competitive process between aflibercept and ranibizumab for second line treatment of wAMD, and that the Committee would reconsider its view on funding a 3<sup>rd</sup> line anti-VEGF agent after the competitive process had been run.

13.8 The Committee noted that Bayer sent correspondence to PHARMAC in response to the February 2015 PTAC minutes, and that this correspondence was reviewed by PTAC at its August 2015 meeting. The Committee noted that its views, at that time, were unchanged and that PHARMAC should progress with the competitive progress.

13.9 The Committee noted in September 2016, PHARMAC consulted on a proposal to fund ranibizumab second line and aflibercept third line for the use in the treatment of wAMD subject to restriction criteria as recommended by the Ophthalmology Subcommittee and PTAC. The Committee noted that consultation feedback included a strong preference from some clinicians for aflibercept to be the second line treatment listed for wAMD, rather than ranibizumab as proposed and that some responders included evidence to support their views that PHARMAC had not previously considered. The Committee noted

that following review of all the consultation feedback the PHARMAC Board resolved to not accept any proposal. The Committee noted that PHARMAC was now seeking further advice from PTAC on the issues raised in consultation feedback and any evidence not previously considered.

- 13.10 The Committee noted that past PTAC and Subcommittee meetings have already discussed the health need of wAMD, its epidemiology, risk factors, impact on Māori and other populations, and the availability and suitability of current treatments.
- 13.11 The Committee noted the currently funded treatments listed on the HML for wAMD are intravitreal bevacizumab and intravitreal ranibizumab. Members noted that aflibercept is another anti-VEGF agent with a different molecular structure and mechanism of action to either bevacizumab or ranibizumab in that it binds to both vascular endothelial growth factor-A (VEGF-A), placental growth factor (P1GF), and the anti-angiogenic factor galectin-1. Members considered that the difference in aflibercept's growth factor binding profile gives it a theoretical point of difference compared to the other anti-VEGF agents, bevacizumab and ranibizumab, for ophthalmic use which may partially explain its observed effectiveness when used as an additional line of treatment following those anti-VEGF agents.
- 13.12 The Committee noted a recently published study by Wecker et al 2017 (Br J Ophthalmol;101:353-9) that reported the disease progression of wAMD that had been treated with anti-VEGF agents. The Committee noted that despite treatment, the authors reported a gradual decline in visual acuity over time and that approximately 34% of patients at year 5 reported significant visual acuity loss of greater than 15 letters. The Committee considered that the eventual decline in visual acuity in treated patients would mean that patients would eventually progress through the treatment options, from one anti-VEGF agent to another. The Committee noted that the decline in visual acuity in treated wAMD patients is considerably greater than other ophthalmic conditions where anti-VEGF agents were also used (such as diabetic macular oedema, retinal vein occlusion, and myopic choroidal neovascularization).
- 13.13 The Committee noted the new evidence provided by the supplier of aflibercept, Bayer. The Committee noted the longer-term data from the VIEW1 trial (Kaiser et al, Ophthalmology Retina 2017; 1: 304-13) as well as a post-hoc analysis of VIEW1 and VIEW2 trials (Jaffe et al, Ophthalmology 2016;123:1856-64). The Committee noted that both the VIEW1 and VIEW2 studies have previously been considered by PTAC, and noted that patients in those trials were treatment naïve, and have different characteristics to the population likely to receive treatment with aflibercept in New Zealand. The Committee therefore considered the applicability and generalisability of those trial results to the New Zealand setting is limited. The Committee noted interim results from two ongoing real world observational studies provided by Bayer (RAINBOW and PERSEUS, unpublished data provided by supplier) which compared the effectiveness and injection frequency with what was observed in the results of the VIEW1 and VIEW2 studies. The Committee noted that the RAINBOW trial was also conducted in treatment naïve patients and approximately half of patients in the PERSEUS trial were treatment naïve, and considered that their relevance to the New Zealand setting is uncertain.
- 13.14 The Committee noted that there were no high quality, randomised controlled, head-to-head studies looking at the use of aflibercept versus ranibizumab in the second line setting. The Committee noted that, in the New Zealand context, evidence was limited to smaller, lower quality studies looking at the use of ranibizumab and aflibercept in either the second or third line setting.
- 13.15 The Committee reviewed Moisseiev et al 2015 (RETINA; 35:1323-30), De Gues et al 2013 (Acta Ophthalmologica; 91:411-3), and Kaiser et al 2012 (Ophthalmic Surg Lasers Imaging; 43:13-9), which looked at the benefits of ranibizumab in the second line setting after patients had switched from bevacizumab. The Committee noted that both Moisseiev et al (2015) and De Gues et al (2013) were retrospective analyses, where patients who

had switched from bevacizumab to ranibizumab were identified and their medical records retrospectively reviewed, and that Kaiser et al was a cohort study. The Committee noted that none of the studies showed a statistically significant change in visual acuity at the end of follow up after switching to ranibizumab, and that only De Gues et al 2013 showed significant improvements in anatomical changes on optical coherence tomography (OCT), but did not elaborate on what these anatomical changes were.

- 13.16 The Committee noted that there was new evidence published since PTAC's 2015 review on the effects of switching to aflibercept after treatment failure with either bevacizumab, ranibizumab, or both. The Committee noted two meta-analyses, Spooner et al 2017 (Clin Ophthalmol 11:161-77) and Seguin-Greenstein et al 2016 (J Ophthalmol. 2016;4095852) analysing the effectiveness of aflibercept in patients who had switched from bevacizumab and/or ranibizumab. The Committee also noted that Spooner et al (2017) included 28 studies and that Seguin-Greenstein et al (2016) included 7 studies that had also been included in the Spooner et al analysis. The Committee noted that patient baseline characteristics were similar in the Spooner et al meta-analysis. Mean age ranged from 70.1 to 83.4 years, baseline best corrected visual acuity (BCVA) ranged from 42.50 to 74.20 ETDRS letters (a measure of visual acuity which replaces the Snellen and Sloan tests), and the mean central retinal thickness (CRT) ranged from 228.60 to 449.00  $\mu\text{m}$ . The Committee considered that the meta-analysis by Spooner et al (2017) included patients whose eyes had advanced disease and were poor responders to bevacizumab and ranibizumab.
- 13.17 The Committee noted that Spooner et al. (2017) included 19 studies assessing the change in BCVA between baseline and 6 months, and noted that the pooled results found a mean increase of 1.11 letters although this increase was not statistically significant (95% CI -0.25 to 2.46,  $P=0.11$ ). Of the 15 studies included which assessed the change in BCVA over 12 months, a non-significant mean increase of 0.63 letters was found (95% CI -0.26 to 1.52,  $P=0.17$ ). The Committee noted that different treatment regimens had different outcomes in BCVA improvement. In terms of central retinal thickness (CRT), the Committee considered that switching to aflibercept caused a significant reduction in CRT from baseline with a mean reduction of 61.90  $\mu\text{m}$  (95% CI -77.10 to -46.80,  $P<0.001$ ). The Committee considered that anatomical and structural improvements in the eye were associated with the preservation of vision.
- 13.18 The Committee also noted a study by Zhu et al 2016 (Graefes Arch Clin Exp Ophthalmol 255:475-84) assessing the vision-related quality of life in patients treated with 12 months of aflibercept in treatment resistant wAMD. The Committee noted that patient's quality of life (measured using the NEI VFQ-25 composite score) was significantly impacted by changes in the visual acuity score as it affects the patient's ability to be mobile, self-care, and conduct usual daily activities. The Committee however noted that there was no evidence to suggest that structural changes in anatomical central macular thickness alone, would impact quality of life.
- 13.19 Members noted a conference abstract by Kiss et al (2016) which reviewed the likely frequency of injections with aflibercept in the real-world setting. The authors of this 2-year claims based analysis reported that the real world treatment patterns for treatment-naïve and previously-treated patients, given ranibizumab or aflibercept for wAMD, are comparable in regards to the mean injection frequency (5.4 vs 5.4 mean injections over 12 months, and 7.6 vs 8.1 over 24 months for ranibizumab and aflibercept respectively in treatment naïve patients, and 5.7 vs 5.8 mean injections over 12 months, and 9.3 vs 9.6 over 24 months for ranibizumab and aflibercept respectively in previously treated patients).
- 13.20 The Committee considered that cumulative evidence from first line treatment trials continues to support the notion that bevacizumab, ranibizumab and aflibercept have similar safety and efficacy in wAMD. The Committee considered that there was no robust evidence to support the notion that there would likely be fewer injections (increased time between injections) with aflibercept compared with ranibizumab in the second or third line

setting, and that the amount of injections required for both agents was likely to be similar. The Committee highlighted concerns that DHB ophthalmology services are already significantly stretched and that should aflibercept be funded second line, that it is likely that additional resource would be needed.

- 13.21 The Committee considered that whilst the quality of evidence for second line use for both ranibizumab and aflibercept is moderate to poor, both the quantity and quality of evidence is higher for studies using aflibercept than ranibizumab in the second line setting. The Committee considered that given the uncertainty with regards to the therapeutic equivalence of the two agents in the second line setting that it would not be appropriate to run another RFP for a second line agent in wAMD. The Committee noted that ranibizumab is currently listed in the HML with restrictions, as the second line anti-VEGF agent. The Committee considered that if only one anti-VEGF agent were to be funded for second line treatment, that aflibercept would be the preferred agent. The Committee recommended that aflibercept be funded with a medium priority for use in the second line setting for treatment of wAMD.
- 13.22 The Committee reviewed the recommendation from the 2014 Ophthalmology Subcommittee that depending on the choice of second line anti-VEGF agent, another anti-VEGF agent would be needed for those patients who are pregnant or have recently had a MI or stroke. The Committee considered that there is currently no evidence to support that the risks to pregnant women or patients with a recent myocardial infarction or stroke are different with different anti-VEGF agents. However, the Committee considered that ranibizumab may theoretically be safer in pregnancy than aflibercept and bevacizumab due to the mechanism of action and concerns with systemic absorption, and therefore it may be required for first line anti-VEGF use in this specific patient population. The Committee considered that this patient group (pregnant people requiring a first line treatment) would be likely to be small. With regards to patients who have recently had a MI or stroke the Committee considered that the systemic effects of all anti-VEGF agents are similar, that no one agent is safer than the other. The Committee recommended that funding of a third line agent for wAMD be declined.
- 13.23 The Committee noted the wording of the restriction to the currently listed second line anti-VEGF agent in Section H of the Pharmaceutical Schedule. The Committee noted that the current continuation criteria required patients to re-trial with bevacizumab to demonstrate on-going non-response, and noted that this criterion was recommended previously by the Ophthalmology Subcommittee to help manage fiscal risk. The Committee considered that there is no evidence to support the inclusion of the re-trial criterion. The Committee considered that there should be objective measurements included in the entry criteria, and that exit criteria should also be developed. The Committee considered that the use of visual acuity may provide an objective measure for an exit criterion. The Committee recommended that the Ophthalmology Subcommittee review the restriction for second line anti-VEGF agent, specifically the criteria for re-trial with bevacizumab, and that the Subcommittee develop objective entry and exit criteria.

### 3. Ranibizumab for 2nd line DMO

#### Application

- 13.24 The Committee considered an application from Novartis NZ Limited for the listing of ranibizumab on the Hospital Medicines List (HML) as second line treatment of diabetic macular oedema (DMO) after bevacizumab.

#### Recommendation

- 13.25 The Committee **recommended** that ranibizumab be listed on the HML as a second line anti-VEGF treatment for diabetic macular oedema with a **low** priority.
- 13.26 The Committee **recommended** that a third line anti-VEGF agent for the treatment of DMO be **declined**.

- 13.27 The Committee **recommended** that the proposed access criteria to second line treatment for DMO be referred to the Ophthalmology Subcommittee for further development, including objective entry and exit criteria.

## Discussion

- 13.28 The Committee noted that aflibercept, another anti-VEGF agent, had previously been considered by PTAC for the treatment of diabetic macular oedema (DMO) at its meeting in November 2015, where it was recommended that first line aflibercept for the treatment of DMO be declined and that the Ophthalmology Subcommittee consider aflibercept as second line anti-VEGF treatment for DMO at its next meeting. The Committee noted the February 2016 Ophthalmology Subcommittee's recommendation where it also recommended that aflibercept for first line anti-VEGF treatment for DMO be declined, and that aflibercept be funded as second line anti-VEGF treatment for DMO with a high priority subject to restrictions.
- 13.29 The Committee noted that DMO is a serious complication of type 1 and 2 diabetes with significant morbidity. The Committee noted diabetic retinopathy shows a gradual and slow progression but that with DMO there is the potential for visual recovery, unlike wet age related macular degeneration (wAMD) where the disease onset and progression is often rapid. Members considered patients who still had good potential for visual recovery were those with no chronic or irreversible retina structural damage, with an initial visual acuity of 6/9 to 6/36. The Committee noted a recent retrospective study by Wecker et al 2017 (Br J Ophthalmol;101:353-9) which reported the disease progression of DMO in 333 individuals that had been treated with anti-VEGF agents. The Committee noted visual acuity (VA) stabilisation in 62% of DMO study patients at year five, and that a similar proportion of patients (19%) had both gained and lost >15 letters. There was no systematic difference in VA outcomes for patients receiving different anti-VEGF agents (bevacizumab, ranibizumab or aflibercept).
- 13.30 The Committee noted that uncontrolled DMO eventually leads to blindness, which affects the person's ability to be mobile, self-care, and usual daily activities. Members noted that blind patients will likely require a very high level of carer support for the most basic activities from dressing to cleaning, cooking and feeding. The level of support may reduce over time as the person adapts and learns to cope with blindness. The Committee reviewed a paper by Khan et al 2016 (Adv Med. 2016:4683427) which reported the degree of burden and the proportion at risk for depression among individuals who provide care to visually impaired patients in a Canadian population. The Committee noted that individuals providing care to patients who were legally blind experienced a higher burden than those providing care to patients with low vision (who were not legally blind). In terms of caregiver depression, the Committee noted that there was a 7.45-fold difference in the odds of depression in caregivers who spent >2.5 hours of caregiving compared to those providing <2.5 hours of caregiving. The Committee noted that it was the duration of caregiving, rather than the extent of vision loss which affected the caregivers' risk of depression.
- 13.31 The Committee noted the prevalence of diabetes in Māori, Pacific Island and Indo-Asian populations was 2 to 3 times higher than Europeans, and that Māori had higher rates of diabetic retinopathy and maculopathy compared with non-Māori (Papali'i-Curtin et al, NZ Med J 2013;126:1383-8). The prognosis of these patients was associated with their diabetic control, and a regression of disease was often seen in patients with a reduced HbA1c. The Committee noted the incidence and prevalence of DMO was likely to increase in the future as the number of patients with type 2 diabetes increases. The Committee considered approximately 10% of diabetic patients would develop DMO in their lifetime, and approximately 10% of patients requiring anti-VEGF treatment for centre-involving diabetic macular oedema would not respond to the currently listed first-line agent; bevacizumab.
- 13.32 The Committee noted the currently funded treatments for DMO are laser therapy and intravitreal bevacizumab, which is listed on the HML for ocular neovascularisation or

exudative ocular angiopathy. Members noted that laser therapy is effective at preserving vision but less effective at restoring lost vision. Members also noted that the use of bevacizumab in DMO is similar to that in wet age-related macular degeneration (wAMD), in that it is an off-label indication and is often administered using a “treat and extend” protocol where the effect of one intravitreal injection of bevacizumab 1.25 mg can last up to 8 weeks. Members noted that in patients for whom bevacizumab is not considered appropriate e.g. pregnant women or women of child bearing potential, patients with recent MI or stroke; triamcinolone injections were currently being used.

#### Ranibizumab as 2nd line anti-VEGF for treatment of diabetic macular oedema (DMO)

13.33 The Committee noted the evidence provided by Novartis supporting the use of ranibizumab in DMO, and the noted the following phase III trials:

- RESTORE study (Mitchel et al, Ophthalmology 2011;118:615-25) and RESTORE extension study (Lang et al, Ophthalmology 2013;120:2004-12)
- RETAIN study (Prunte et al, Br J Ophthalmol 2016;100:787-95)
- Diabetic Retinopathy Clinical Research Network (DRCR.net) study (Elman et al, Ophthalmology 2010;117:1064-77)
- RISE and RIDE studies (Nguyen et al, Ophthalmology 2012;119:789-801) and the long term 36-month results of RISE and RIDE studies (Brown et al, Ophthalmology 2013;120:2013-22)
- REVEAL study (Ishibashi et al, Ophthalmology 2015;122:1402-15)

13.34 The Committee noted that the evidence provided showed that ranibizumab is an effective treatment for DMO in the first line setting versus placebo or laser therapy. However, the Committee considered that the trials had low relevance to the New Zealand setting as patients in New Zealand would have been pre-treated with bevacizumab.

13.35 The Committee noted the following papers looking at the effectiveness of ranibizumab after switching from bevacizumab:

- Katz et al. Eur J Ophthalmol 2017;27:210-4.
- Lee et al. J Ocul Pharmacol Ther 2016;32:659-64.
- Hanhart et al. Case Rep Ophthalmol 2015;6:44-50.
- Fechter et al. Ophthalmic Surg Lasers Imaging Retina 2016;47:1030-7

13.36 The Committee noted that studies by Katz et al (2017), Lee et al (2016), and Hanhart et al (2015) showed statistically significant improvement in the CRT, but not in visual acuity. The Committee noted Fechter et al (2016), an open-label prospective study evaluating the safety and efficacy of 0.3mg ranibizumab in 30 eyes with DMO after recent, chronic and frequent bevacizumab. In this study the authors reported an overall increase in using Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) score from baseline of +6.5 letters +/- 10.18 (unsure statistical significance) at one year and an overall reduction in central subfield thickness (CST) of -115.57 +/- 136.50 at one year. Members noted that this study also provides evidence that as required (PRN) treatments of ranibizumab are as effective as more frequent injections ('sustained') in the second line context.

13.37 The Committee considered that most trials showed that treating with ranibizumab after switching from bevacizumab results in structural improvements, and that only the Fechter et al (2016) study also reported improvements in visual acuity. The Committee considered

that both the quality and strength of evidence for second line ranibizumab for DMO was low.

- 13.38 The Committee considered that in patients who do not respond to, or tolerate bevacizumab, that there is an unmet health need for a second line anti-VEGF agent. The Committee considered that ranibizumab may work to address this health need, and recommended that this be funded as second line treatment with a low priority.

#### Anti-VEGFs for 2nd and 3rd line treatment of DMO

- 13.39 The Committee noted that both aflibercept and ranibizumab are anti-VEGF agents registered for the treatment of DMO. The Committee noted the relative benefit of using either ranibizumab or aflibercept in the second line setting.

- 13.40 The Committee noted the following studies assessing the effectiveness of aflibercept after switching from bevacizumab and/or ranibizumab.

- Bahrami et al, AJO 2016;164:118-27
- Klein et al, Int J Retina Vitreous 2017;3:16
- Lim et al, Clin Ophthalmol 2015;9:1715-8
- Mira et al, J Ophthalmol 2017:5632634

- 13.41 Four abstracts from the 2016 Annual meeting of the Associated for Research in Vision and Ophthalmology (ARVO) - Rahimy et al (B0303), Sadowsky et al (B0336), Ores et al (B0339), and Cunningham et al (B0309).

- 13.42 The Committee reviewed a Danish study by Vorum et al (Curr Med Res Opin 2016;32:1943-50) which investigated real world evidence for injection frequency after switching from ranibizumab to aflibercept in DMO and other indications. There was an expectation that the number of injections would reduce due to the perception of prolonged treatment duration with aflibercept. The Committee considered that the study failed to demonstrate a reduction in injection frequency after the switch, and that this finding was consistent with analysis of data reported by Wecker et al (2017) reporting an average of 6 injections of anti-VEGF treatment each year.

- 13.43 The Committee noted that there are no high quality comparative studies available to determine the need, or preferred line of therapy for anti-VEGF treatment in patients with DMO. The Committee noted that there is some level three evidence, from non-experimental studies, suggesting that both ranibizumab and aflibercept provide structural and variable functional benefit in patients resistant to or for whom bevacizumab treatment was failing.

- 13.44 The Committee considered that there is a need for a second line agent in the treatment of DMO but there is not convincing evidence that it should be ranibizumab rather than aflibercept. The Committee considered that from the low quality data available, it is not clear that ranibizumab and aflibercept are therapeutically equivalent in the second line context.

- 13.45 The Committee considered that if there was only one second line agent funded, that there is both more evidence and stronger evidence for aflibercept than ranibizumab. The Committee considered that improvements typically seen with aflibercept were in the third line setting (following bevacizumab and ranibizumab) after ranibizumab has already been trialed and failed, and therefore aflibercept would likely be superior to ranibizumab.

- 13.46 The Committee highlighted concerns that DHB ophthalmology services are already significantly stretched and that should aflibercept be funded second line for DMO that it is likely that additional resource would be needed.
- 13.47 The Committee considered that the evidence for third line anti-VEGF agent for DMO was poor. The Committee recommended that a third line anti-VEGF agent for the treatment of DMO be declined.
- 13.48 The Committee considered that the access criteria previously recommended by the Ophthalmology Subcommittee for aflibercept for DMO would be applicable to either agent for second line use in DMO, however considered these criteria should be developed further to include measures of functional and anatomical benefit from ongoing treatment and an explicit end-point to ensure treatment is not continued when there is only minimal benefit to gain.

## 8 . Elbasvir/grazoprevir – Hepatitis C genotype 1

### Application

- 8.1 The Committee considered the application from MSD for elbasvir/grazoprevir (Zepatier) for the treatment of chronic hepatitis C genotypes 1, 3 (in combination with sofosbuvir) and 4.

### Recommendation

- 8.2 The Committee **recommended** that the application from MSD for the funding of Zepatier for the treatment of chronic hepatitis C genotypes 1, 3 and 4 be **declined**.
- 8.3 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

### Discussion

- 8.4 The Committee noted that Viekira Pak (paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets copackaged with dasabuvir 250 mg tablets) has been funded without restriction for the treatment of hepatitis C virus (HCV) genotype 1 since 1 July 2016.
- 8.5 Members noted that the application for funding of Zepatier was for the treatment of chronic hepatitis C genotypes 1, 3 and 4, and noted that the secondary application was for the people who inject drugs (PWID) population or who remain unsuitable for treatment with Viekira Pak.
- 8.6 The Committee reviewed the current guidelines for treatment with Viekira Pak and noted that ribavirin is co-prescribed for patients with HCV genotype 1a, accounting for approximately 85% of all prescriptions. The Committee noted that the success rate of Viekira Pak is 96-97% and is higher than the efficacy reported for Zepatier.
- 8.7 Members noted the evolution of treatment with Viekira Pak in New Zealand since its funding for genotype 1 patients and noted that treatment has shown to be successful in both primary and secondary care. Members noted 2-5% of patients have virologic failure with Viekira Pak.
- 8.8 The Committee noted that between 10 and 15% of HCV genotype-1 infected patients without prior exposure to NS5A inhibitors have detectable HCV NS5A resistance-associated variants (RAVs); for patients infected with genotype-1a, the presence of RAVs cause a 5-fold reduction in the activity of NS5A inhibitors. Since elbasvir is a NS5A inhibitor, Members noted that both the AASLD (American Association for the Study of Liver Diseases) and EASL (European Association for the Study of the Liver) recommend testing for baseline RAVs before commencing with treatment with Zepatier. If RAVs are present in genotype 1a infected individuals without cirrhosis, a modified treatment protocol of Zepatier in combination with ribavirin for 16 weeks is recommended.
- 8.9 The Committee noted that there is an unmet clinical need for treatment for patients with more severe hepatic impairments beyond Child-Pugh A but without MELD scores  $\geq 15$  (ie Child-Pugh B and C with MELD scores  $< 15$ ), noting that these patients would be not eligible (Child-Pugh B) or contraindicated (Child-Pugh C) for treatment with Viekira Pak (confined to Child-Pugh A mild hepatic impairment) and not eligible for funded Harvoni treatment (confined to MELD scores  $\geq 15$ ).
- 8.10 The Committee noted that Zepatier was evaluated in two phase III trials, and numerous phase II trials, including studies that address patient sub-groups. Members reviewed the results of the C-WORTHY (Sulkowski, M., et al. Lancet. 2015; 385:1087-97; Lawitz, E., et al. Lancet. 2105; 358:1075-86) and C-Salvage (Forns, X., et al. Liver Int. 2015; 35(:2358-

- 62) phase II trials, and noted that Zepatier was effective in both cirrhotic and non-cirrhotic genotype 1 patients. A 97% (28/29) SVR12 rate was demonstrated in genotype 1 cirrhotic treatment-naïve patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase II C-WORTHY trial.
- 8.11 The Committee noted that the safety and efficacy of Zepatier was evaluated in two pivotal Phase III trials: the C-EDGE Naïve trial (Zeuzem, S., et al. *Ann Intern Med.* 2015; 163:1-13) and the C-EDGE Treatment Experienced trial (Kwo, P., et al. *Gastroenterology.* 2017; 152 :164-75). Members noted that unquantifiable HCV RNA 12 weeks after the end of study treatment (SVR12) of Zepatier was 92% in treatment naïve patients with HCV genotype 1a infection and 99% in genotype 1b after 12 weeks of treatment. The Committee noted that the SVR12 for treatment experienced patients following 12 weeks of Zepatier was 92.4% in these genotypes.
- 8.12 The Committee reviewed the results of the C-SWIFT study (Lawitz, E., et al. *Hepatology.* 2017; 65:439-50) that evaluated the efficacy of Zepatier in treatment-naïve patients with chronic HCV genotype 1 or 3 infection. Members noted that for treatment of genotype 3 patients, Zepatier must be combined with sofosbuvir 400 mg. The Committee noted that the SVR12 following 12 weeks of combined treatment for genotype 3 patients was 93%. However, members noted that this treatment regime is not feasible since sofosbuvir alone is not available in New Zealand and has a high cost. The Committee noted that Zepatier is effective for genotype 4 patients, but acknowledged that this patient group can also be treated with Viekira Pak and Ribavirin.
- 8.13 Members reviewed the results of the C-EDGE CO-STAR study (Dore, G., et al. *Ann Intern Med.* 2016;165:625-34) that evaluated the efficacy of Zepatier in people who inject drugs (PWID) with genotype 1, 4 or 6 who were at minimum 80% adherent to visits for opioid-agonist therapy. Patients were randomized to receive immediate treatment or deferred treatment; the SVR12 was 91.5% in the immediate treatment group and 89.5% in the active-phase deferred treatment group. The Committee noted that the authors should be commended for targeting their study to treat this group of patients.
- 8.14 The Committee considered that 80% of new infections are in PWID, which is estimated at 1000 new cases per year. Members noted that the continued number of new cases will depend on the number of individuals identified and treated in this population, as well as the success of needle exchange programs, which can reduce infection rates by 40-50%. The Committee noted that these patients are currently being managed with funded treatment and that there is no evidence that PWID would be more adherent to a single tablet regimen. Members also noted that adherence in PWID may be different in New Zealand because patients are seen regularly through opiate substitution treatment services.
- 8.15 The Committee noted that there was no efficacy advantage of Zepatier compared to Viekira Pak, but there were some suitability advantages, including a single daily tablet regimen, no requirement for ribavirin in most patients (except genotype 1 resistance associated variant patients) and less drug-drug interactions. Members considered that there were several disadvantages, noting that Zepatier is also contraindicated with cirrhosis and Child Pugh Turcotte B/C i.e., decompensated cirrhosis, and significantly, all patients need liver function test (LFT) monitoring regardless of stage of liver disease, since 1% of patients have more than 5 times increase in ALT levels on treatment. NS5A RAV testing would also be required. In contrast, for Viekira Pak, LFT monitoring is only required in cirrhotic patients. Members also noted that the SVR12 is only 50% in HCV genotype 1a patients who have baseline NS5A resistance associated variants (RAVs), with this estimated to be approximately 15% of patients.
- 8.16 The Committee noted that new pangenotypic HCV treatments are likely to become available in the near future.

