PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 21 & 22 February 2019

Minutes of PTAC and Subcommittees of PTAC 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 meeting; only the relevant portions of the minutes relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of 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

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Giles Newton Howes
Ian Hosford
Jennifer Martin
Matthew Strother
Melissa Copland
Simon Wynn Thomas
Stephen Munn
Tim Stokes

1. Subcommittee Minutes

Gastrointestinal Subcommittee

Ustekinumab for Crohn's disease

1.1 The Committee noted that the Subcommittee had recommended a different priority than PTAC for ustekinumab for the treatment of Crohn's disease. PTAC had previously recommended that ustekinumab be listed for Crohn's disease, in patients where a TNF inhibitor has failed, with a medium priority, while the Subcommittee had recommended that ustekinumab be listed for the same group but with a high priority.

1.2 The Committee noted that the Subcommittee's higher priority recommendation was based on a lack of alternatives for patients in this circumstance, as well as the high health need. The Committee also noted that the Subcommittee were concerned about the current unavailability of vedolizumab (an integrin α4β7 inhibitor) which it considered would be a more effective agent.

1.3 The Committee considered its previous recommendation was based on a review of the same information and evidence available to the Subcommittee. The Committee considered that the Subcommittee had not identified new evidence that PTAC had not previously considered.

1.4 The Committee did not accept the Subcommittee's recommendation on ustekinumab for Crohn's disease. The Committee **recommended** again that ustekinumab be listed for Crohn's disease, in patients where a TNF inhibitor has failed, with a medium priority. The Committee noted, however, that the views regarding health need and recommendation of the Subcommittee also be presented when prioritising this proposal against other funding options.

Adalimumab for ulcerative colitis

1.5 The Committee noted that the Subcommittee had recommended that listing adalimumab for the treatment of ulcerative colitis as a second biologic treatment in patients who were non-responders to infliximab with a high priority, and that PTAC had recommended adalimumab for the same indication with a low priority.

1.6 The Committee noted that the Subcommittee made a high priority recommendation in part because of the unavailability of vedolizumab. The Committee noted that PHARMAC had undertaken an economic analysis for vedolizumab and the proposal had been ranked against other investments. The Committee noted that it had asked PHARMAC to invite the supplier to make an application and that that application should be brought to PTAC to review when received, and noted that while PHARMAC has been attempting to work with the supplier, no application has yet been received.

1.7 The Committee did not accept the Subcommittee's high priority recommendation on adalimumab for ulcerative colitis and **recommended** again that adalimumab be listed for treatment of ulcerative colitis as a second-line biologic treatment in patients who were non-responders to infliximab with a low priority.

1.8 The Committee also **recommended** again that the application for adalimumab for first biologic line treatment of ulcerative colitis be deferred until PHARMAC staff report back to PTAC on the availability of infliximab in each DHB.

1.9 The Committee also **recommended** that it be presented a full paper on vedolizumab, and that it could reconsider its advice on vedolizumab, and also on other applications, following that paper.

Loperamide

1.10 The Committee noted and accepted the Subcommittee's recommendation on loperamide.

Therapeutic drug monitoring of biologics for gastrointestinal indications

1.11 The Committee noted that the Subcommittee had reviewed an application for higher doses of infliximab and adalimumab for gastrointestinal indications, using therapeutic drug monitoring to support dose changes, and that it had made two recommendations on the matter.

1.12 Committee members considered that there was evidence to support higher doses in some patients determined by therapeutic drug monitoring, and also evidence that some patients may be under-dosed with current Special Authority restrictions. However, members considered there was considerable uncertainty as to the benefits of this approach, as well as the extent to which the approach would change use of infliximab and adalimumab, due to the lower quality of the evidence available.

1.13 The Committee discussed whether incorporating therapeutic drug monitoring could have benefits in areas outside of gastrointestinal medicine.

1.14 The Committee did not accept the recommendations from the Subcommittee around therapeutic drug monitoring. The Committee **recommended** that PHARMAC bring a paper to PTAC on therapeutic drug monitoring of biologics for gastrointestinal conditions.

Widening access of budesonide capsules for non-cirrhotic autoimmune hepatitis

1.15 The Committee noted and accepted the Subcommittee's recommendation for budesonide capsules for non-cirrhotic autoimmune hepatitis.

Budesonide 9 mg controlled release for ulcerative colitis

1.16 The Committee noted that the Subcommittee had reviewed an application for budesonide 9 mg controlled release capsules for ulcerative colitis, and that the Subcommittee had recommended funding this with a medium priority, subject to Special Authority criteria as set out in its minutes.

1.17 Members considered that the new presentation was a modest reworking of an existing formulation and that the evidence to support the proposal was of poor quality. It was also unclear if it had been compared to a comparator commonly used in New Zealand. Members considered the main advantage appeared to be avoidance of other systemic glucocorticoid steroid side-effects. Members considered that the proposal would likely have a large cost.

1.18 The Committee did not accept the recommendations from the Subcommittee on budesonide 9 mg controlled release capsules. The Committee **recommended** that PHARMAC bring a paper to PTAC on budesonide 9 mg controlled release capsules for it to consider.

Multivitamin with trace elements for before and after bariatric surgery

1.19 The Committee noted and accepted the Subcommittee's recommendation for multivitamins with trace elements.

Prucalopride for constipation

1.20 PTAC noted that the Subcommittee had recommended that prucalopride be funded for patients with chronic slow-transit constipation with a medium priority, subject to criteria set out in the Subcommittee minutes.

1.21 PTAC considered this was potentially a very large group of patients, some of whom might have a serious health need. The Committee noted that the evidence reviewed by the Subcommittee suggested that prucalopride has a modest effect. PTAC considered that requiring a gastroenterologist be involved in the Special Authority was a considerable access barrier given the common nature of the condition and the limited number of gastroenterologists. Other than the issue of accessing a gastroenterologist, PTAC considered that the suggested Special Authority criteria were overly permissive and would be a fiscal risk given the high use of laxatives in the general population and older adults in particular, if these were the only other criteria for access.

1.22 The Committee did not accept the Subcommittee's recommendation on prucalopride. Instead, PTAC **recommended** that PHARMAC bring a paper on prucalopride to PTAC.

Tacrolimus suppositories for rectal inflammation due to inflammatory bowel disorders

1.23 PTAC noted that the Subcommittee had recommended that tacrolimus suppositories be funded, without restriction, with a high priority.

1.24 PTAC considered that it was unclear what the costs of this proposal would be, as a process for compounding and distributing tacrolimus suppositories had not yet been developed.

1.25 PTAC considered that more information was needed to provide advice about this proposal and so did not accept the Subcommittee's recommendation. The Committee **recommended** that PHARMAC research the costs of providing tacrolimus suppositories and bring this information to PTAC for a recommendation about priority for funding.

Rare Disorders Subcommittee

1.26 The Committee considered the record of newly established Rare Disorders Subcommittee meeting held 5 & 6 November 2018, where 13 funding applications were considered for 10 medicines.

1.27 The Committee noted and accepted the Subcommittee recommendations in paragraph 4.4 and 4.5 that carglumic acid be funded with a high priority for the treatment of hyperammonaemia due to carbamoyl phosphate synthetase 1 (CPS1) or N-acetylglutamate synthase (NAGS) deficiency based on high health need, a lack of treatment options, and moderate evidence of benefit, subject to Special Authority criteria; and funded with a medium priority for the treatment of hyperammonaemia during an acute decompensation episode due to organic acidaemias based on high health need and moderate evidence of benefit, subject to Special Authority criteria.

1.28 The Committee noted the reasons for the different priority between these two indications were largely based on the availability of some funded alternatives for patients with organic acidaemias. The Committee noted there may be other uses for carglumic acid in terms of treating hyperammonaemia related to other conditions, however, members considered the proposed Special Authority criteria appropriately managed the risk of use in other indications.

1.29 The Committee noted and accepted the Subcommittee recommendation in paragraph 7.4 that nitisinone be funded with a high priority for the treatment of hereditary tyrosinaemia type 1 (HT-1) due to high health need, lack of treatment options, and moderate evidence of benefit, subject to Special Authority criteria. The Committee considered that patient monitoring for hepatocellular carcinoma would be still required if nitisinone was to be funded for HT-1, and that liver transplant would still be required for some HT-1 patients.

1.30 The Committee noted and accepted the Subcommittee recommendations in paragraph 6.4 and 6.5 to defer consideration of nusinersen for spinal muscular atrophy type I, type II and IIIa until longer-term follow-up analyses are published from the SHINE and NURTURE trials.

1.31 The Committee considered that the nusinersen trials were of good quality and the short-term outcomes reported were promising; however, the outcome of sustained preservation of function and motor milestones needs to be demonstrated in long-term data to inform a recommendation. The Committee considered that it was difficult to make a recommendation based on trials with short duration.

1.32 The Committee noted the high health need of patients and families living with SMA and the high level of consumer interest in nusinersen. Members acknowledged the many personal submissions that were considered by the Subcommittee describing the impact of SMA. The Committee considered that the expectations of benefit are not supported by the currently available evidence for nusinersen in SMA due to the short-term duration of the clinical trials.

1.33 The Committee noted that interim analyses of the NUTURE and SHINE trials were expected to be published later this year. The Committee recommended that consideration of interim analyses of the key nusinersen trials (NURTURE and SHINE) should be delegated to the Rare Disorders Subcommittee and the Subcommittee could then consider if this data was sufficiently mature enough to be brought back to PTAC.

1.34 The Committee considered the correspondence provided by Biogen (after the Rare Disorders Subcommittee), the supplier of nusinersen. In response, the Committee noted that the Rare Disorders Subcommittee has considered the evidence, and this has been discussed with PTAC and that there will be continued discussions based on updated analyses. The Committee did not consider it useful for Australian clinicians to present to PTAC as the key evidence Biogen needed to provide was related to clinical benefits from randomised controlled trials and the respective cohort follow on studies that are currently underway.

1.35 The Committee noted and accepted the Subcommittee recommendations in paragraph 5.4 that elosulfase alfa for the treatment of mucopolysaccharidosis type IVA (MPS IVA) be declined based on uncertainty regarding the long-term benefit of treatment and the high proposed cost of the medicine.

1.36 The Committee noted and accepted the Subcommittee recommendations in paragraph 8.4 that migalastat for the treatment of Fabry disease be declined based on insufficient evidence of long-term beneficial effects on morbidity and mortality. Members noted that this application may be reconsidered by the Rare Disorders Subcommittee once the outcome on the recommendation to fund enzyme replacement therapy for Fabry disease has been determined.

1.37 The Committee noted and accepted the Subcommittee recommendations in paragraph 10.4 that miglustat for the treatment of Niemann-Pick disease Type C be declined based on low quality evidence of benefit, and concerns regarding study design including short follow-up and uncertainty regarding the applicability of endpoints to long-term outcomes.

1.38 The Committee noted and accepted the Subcommittee recommendations in paragraph 11.4 that miglustat for the treatment of Type 1 Gaucher disease be declined based on low quality evidence of benefit and the adverse effect profile.

1.39 The Committee noted and accepted the Subcommittee recommendations in paragraph 12.4 that teduglutide for the treatment of short bowel syndrome (SBS) in patients with type III intestinal failure be declined based on the modest evidence of short-term benefit provided by treatment, lack of long-term data, and safety concerns. The Committee noted that there are many aetiologies for SBS and that further advice about this application could be sought from the Gastrointestinal Subcommittee.

1.40 The Committee noted and accepted the Subcommittee recommendations in paragraph 13.4 that alglucosidase alfa for the treatment of late onset Pompe disease be declined based on the uncertainties regarding survival benefit, modest clinical benefits with regards to ambulation and pulmonary function, and the high proposed cost of the medicine.

1.41 The Committee noted the Subcommittee recommendations in paragraph 9.4 and 9.5 regarding recommending funding of enzyme replacement therapy for Fabry disease and noted that the funding application for agalsidase alfa is on the agenda of this meeting and will be considered further by the Committee (see section 10 for the record of the discussion).

1.42 The Committee noted the Subcommittee recommendations in paragraph 14.4 regarding recommending funding of ivacaftor for the treatment of cystic fibrosis in patients with a G551D mutation and noted that a funding application is on the agenda of this meeting and will be considered further by the Committee (see section 9 for the record of the discussion).

1.43 The Committee acknowledged the work of the Subcommittee in thoroughly considering a large number of funding applications at its first meeting.

Cancer Treatments Subcommittee

1.44 The Committee noted and accepted the record of the Cancer Treatments Subcommittee of PTAC held on 21 September 2018, with the exception of item 7, 8 and 14.

1.45 In regards to item 7, lanreotide acetate for gastroenteropancreatic neuroendocrine tumours, the Committee noted the application was on the PTAC agenda for discussion at the current meeting.

1.46 In regards to item 8.5, venetoclax for chronic lymphocytic leukaemia and 17p deletion or TP53 mutations, the Committee noted and accepted CaTSoP's recommendation that venetoclax be funded with a high priority subject to the specified Special Authority criteria. The Committee requested that CaTSoP consider the relative priorities of venetoclax and ibrutinib in this setting.

1.47 In regards to item 8.6 and 8.7, venetoclax for chronic lymphocytic leukaemia relapsed chronic lymphocytic leukaemia (within 12 months of prior therapy) and relapsed chronic lymphocytic leukaemia (12-36 months of prior therapy), the Committee requested that further clarification be sought from CaTSoP on patient numbers in each of these groups, likely improvement in survival (possibly including comparison with historical controls) and commentary on the strength and quality and applicability of the evidence to the New Zealand setting.

1.48 In regards to item 14, palbociclib as initial endocrine therapy for the treatment of hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer, the Committee requested the application be reviewed by PTAC at a future meeting.

Immunisation Subcommittee

1.49 The Committee reviewed the Immunisation Subcommittee minutes from the 18 September 2018 meeting.

1.50 The Committee noted that the Immunisation Subcommittee reviewed a paper from PHARMAC staff about quadrivalent meningococcal ACWY vaccine and made recommendations 5.3 and 5.4. The Committee noted that it was considering a paper from PHARMAC staff about quadrivalent meningococcal ACWY vaccine at this meeting.

1.51 The Committee noted and accepted the remaining recommendations of the Immunisation Subcommittee, 4.3, 5.4, 6.3 and 7.3.

2. Correspondence & Matters Arising

Calcipotriol with betamethasone foam spray

2.1 The Committee noted correspondence from the supplier, Leo Pharma, about the PTAC record of the funding application for calcipotriol with betamethasone foam spray that was considered at the November 2018 PTAC meeting. Members agreed to minor changes to the PTAC minute for this application, as shown below (only affected paragraphs shown; changes in bold and deletions in strikethrough).

> **Calcipotriol with betamethasone foam spray for the treatment of psoriasis vulgaris**
>
> The Committee noted that in these studies a total of 749 patients were treated with the combination foam and 683 patients used a comparator; and that the results showed a consistent modified PASI75 of approximately 50% for the combination foam formulation, 34-40% for the combination gel, 34% for steroid-only in the foam vehicle, and 14% for calcipotriol-only in foam vehicle. Members noted ~~that~~ **the quicker** onset of improvement ~~response was seen at six weeks~~ for the combination foam versus eight weeks for the combination gel, which continued in the extension studies to 12 weeks; however, the Committee considered this was not clinically significant given psoriasis vulgaris was a chronic, incurable condition.
>
> The Committee noted that in the ~~PSO-FAST~~ **PSO-ABLE** study (~~Leonardi C~~ **Paul**, et al.) patients used more foam than gel, although this may reflect patients stopping using the gel. Members noted that the mean total amount of combination foam used from baseline to week 4 was 98.6 grams, whereas the mean total amount of combination gel used from baseline to week 8 was 164.3 grams. Over 12 weeks, the amount of combination foam used was 236.4 grams, whereas the total amount of combination gel used was 193.1 grams.

Deflazacort for Duchenne Muscular Dystrophy

2.2 The Committee noted that in August 2016, PTAC considered a clinician application for deflazacort for treatment of patients with Duchenne muscular dystrophy (DMD) who are unable to tolerate prednisone. The Committee noted that it had recommended the application be declined but that it would like to review its recommendation once the FOR-DMD study (ClinicalTrials.gov Identifier: NCT01603407) was published.

2.3 The Committee considered correspondence from Muscular Dystrophy New Zealand (MDNZ) requesting that consideration be given to a post hoc analysis of the Ataluren Confirmatory Trial (ACT) DMD study (Shieh et al. Muscle Nerve 2018;58:639-45) that had recently been published. The Committee thanked MDNZ for providing this for review. The Committee considered that this trial provided retrospective data (Shieh et al. Muscle Nerve 2018;58:639-

45) and that the evidence did not change the Committee's recommendation for decline. The Committee reiterated that it would like to review its recommendation once the FOR-DMD study (ClinicalTrials.gov Identifier: NCT01603407) was published; noting that this is a randomised controlled trial.

3. Pembrolizumab as a first-line treatment for advanced NSCLC

Application

3.1. The Committee considered the funding of pembrolizumab (Keytruda) as monotherapy for patients with metastatic, unresectable, stage III and IV (advanced) non-small cell lung cancer (NSCLC) whose tumours express programmed death ligand 1 (PD-L1) at a level of ≥ 50% in a first-line setting for EGFR wildtype patients.

Recommendation

3.2. The Committee **recommended** that pembrolizumab as monotherapy be funded with **medium priority** for previously untreated advanced PD-L1 positive EGFR wildtype NSCLC noting that uncertainty remained regarding the magnitude of benefit from treatment in this setting and the current high price of pembrolizumab.

3.3. The Committee **recommended** that advice be sought from CaTSoP regarding: interpretation of the role of pemetrexed use on the reported survival results in the relevant clinical trials; further information regarding interpretation of the clinical significance of HRQoL and OS data in the context of lung cancer patients; consideration of the relative benefit of monotherapy vs chemotherapy particularly in different patient populations (PD-L1 status, histology or other); and appropriate access criteria for pembrolizumab in the treatment of advanced NSCLC.

Discussion

3.4. The Committee considered that the evidence for the use of pembrolizumab monotherapy as a first-line treatment for advanced NSCLC comes mainly from KEYNOTE-024 (Reck et al. NEJM 2016;375:1823) and noted the suppliers application for funding has been considered by PTAC a number of times.

3.5. The Committee noted that previously PTAC had deferred making a recommendation regarding this application due to incomplete or limited evidence about longer-term survival and quality of life.

3.6. The Committee noted that most recently, in August 2018, PTAC deferred making a recommendation until its review of further peer-reviewed published data with regards to longer term follow up and quality of life; and considered that if this was not available then the full unredacted Clinical Study Report (CSR) would likely be required to better assess strength and quality of the evidence for relevant clinical outcomes from KEYNOTE-024.

3.7. The Committee noted additional information had been provided by the supplier to support its application for funding of pembrolizumab as monotherapy as a first-line NSCLC treatment including updated longer-term survival analysis for KEYNOTE-024 published online in the Journal of Clinical Oncology (JCO) in January 2019 (Reck et al. JCO 2019;37:537-46, DOI: 10.1200/JCO.18.00149) and the CSR for overall survival (CSR code P024V02MK3475, database locked 18 August 2017).

3.8. The Committee noted that the supplier appeared not to have yet provided the CSR for QoL (CSR code P024V01MK3475, data of database lock 3 June 2016). However, published HRQoL results were available from KEYNOTE-024 (Brahmer et al. Lancet Oncol. 2017;18:1600).

Health related quality of life (HRQoL)

3.9. The Committee noted QLQ-C30 baseline mean (SD) for pembrolizumab of 62.2 (22.3) and for chemotherapy of 59.9 (22.3) improved to 71.0 (21.1) and 63.7 (20.6) respectively, an estimated difference 7.8 (95% CI 2.9 to 12.8) after 15 weeks. Members considered that results were consistent with improved quality of life over this short time period. The Committee noted that the mean QLQ-C30 was the same in the two groups after 33 weeks but this was difficult to interpret as cross-over occurred in 97/149 (65%) of trial participants.

3.10. The Committee noted that EQ-5D-3L results were only given for the VAS with mean (SD) baseline of 68.7 (21.1) and 69.7 (19.3) improving to 75.5 (17.2) and 72.7 (17.1), estimated difference 3.9 (95% CI -0.7 to 8.4). The Committee noted that Brahmer et al did not provide information about health utilities, although this may be available in the relevant CSR, which had not been provided by the supplier.

3.11. The Committee noted that interpretation of minimally clinically important differences (MCID) for HRQoL scores in lung cancer patients indicated a MCID of between 4 and 9 for QLQ-C30 and 7.5 and 11.5 for EQ-5D-3L VAS (Maringwa et al. Supportive Care in Cancer 2011;19:1753-60 and Pickard et al. Health and Quality of Life Outcomes 2007;5:70).

3.12. The Committee considered that in terms of HRQoL pembrolizumab was reported to provide a moderate short-term positive effect compared to chemotherapy alone but if EQ-5D utilities were available this may improve certainty of the QoL effect.

Overall Survival

3.13. The Committee noted survival results reported in Reck et al. NEJM 2016 at a median follow-up of 11.2 months, that median OS had not been reached in either group, and the estimated OS at 6 months was 80.2% (72.9 to 85.7) in the pembrolizumab arm and 72.4% (64.5-78.9) in the chemotherapy arm (HR for death, 0.60; 95% CI, 0.41 to 0.89; P = 0.005).

3.14. The Committee noted that the published longer-term survival data (Reck et al. JCO 2019;37:537-46, DOI: 10.1200/JCO.18.00149) reported the median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86); and when adjusted for crossover HR improved to 0.49 (95% CI, 0.34 to 0.69). Kaplan-Meier estimates of OS at 12 months for pembrolizumab and chemotherapy were 70.3% (95% CI, 62.3% to 76.9%) and 54.8% (95% CI, 46.4% to 62.4%), respectively.

3.15. The Committee considered that pembrolizumab monotherapy provided a benefit in OS over chemotherapy however the actual magnitude was difficult to determine due to significant crossover.

3.16. The Committee considered that as had been previously noted by PTAC there was very significant adverse event profile in a small number of patients treated with immune checkpoint inhibitors, and that for patients with immune-mediated side effects these required resource intensive multi-disciplinary management.

Comparison with combination evidence

3.17. The Committee noted that, at its meeting in November 2018, PTAC had considered an application for the use of pembrolizumab in combination with chemotherapy as a first-line treatment of metastatic NSCLC with no EGFR or ALK genomic tumour aberrations and recommended funding with medium priority.

3.18. The Committee noted that PTAC had also recommended that the combination use application be referred to Cancer Treatments Subcommittee of PTAC (CaTSoP) for advice regarding the lung cancer treatment landscape, potential placement of pembrolizumab

combination regimens in the treatment paradigm, appropriate Special Authority criteria, and further consideration of use of PD-L1 expression as a biomarker.

3.19. The Committee noted that combination trials had been conducted separately for different NSCLC histology (squamous KEYNOTE-407 and non-squamous KEYNOTE-189) and the PD-L1 status in study participants varied in these trials.

3.20. The Committee considered that interpretation of trial evidence for pembrolizumab as a first-line treatment appeared to indicate there may be a differential effect when use as combination or monotherapy in patients with differing PD-L1 status, although there was no direct evidence of this. The Committee considered the effect of survival appeared to be similar for both NSCLC with squamous and non-squamous histology.

3.21. The Committee considered that based on currently available evidence it was uncertain why the survival advantage observed in KEYNOTE-024 from monotherapy use was similar to the survival advantage of combination therapy observed in KEYNOTE-189 and KEYNOTE-407.

3.22. The Committee considered that one reason for this may be related to the different PD-L1 status populations however, the currently available evidence presented contradictory evidence from subgroup analysis – in that KEYNOTE-189 suggested an improved response rate in PD-L1 high patients whereas this was not seen in KEYNOTE-407. Members noted it was also uncertain how a different distribution of ECOG 0 participants or use of pemetrexed influenced the results observed.

3.23. The Committee considered that the data for pembrolizumab in first-line NSCLC appeared to be incongruent and cast uncertainties on its interpretation in terms of the magnitude of survival benefit in different populations and what, if any advantage combination therapy has over monotherapy.

3.24. The Committee considered that in advanced NSCLC there did not appear to be a long 'tail' of survivors as reported in studies of pembrolizumab in melanoma, although this may be reported with longer-term follow up data.

3.25. The Committee considered that the cost-effectiveness of pembrolizumab as a first-line advanced NSCLC treatment was adversely affected by the pricing currently being sought by the supplier.

4. Ivacaftor for the treatment of Cystic Fibrosis with G551D mutation

Application

4.1. The Committee reviewed the application from Vertex for the funding of ivacaftor for the treatment of cystic fibrosis with G551D mutation.

4.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

4.3. The Committee **recommended** that ivacaftor be funded with a **low priority** for the treatment of cystic fibrosis with the G551D mutation based on high health need, a lack of disease-modifying treatment options, moderate quality evidence of a health benefit noting the limited availability of long-term data, and concerns regarding markers of surrogacy and high cost; subject to Special Authority criteria.

4.4. The Committee **recommended** that advice be sought from the Cystic Fibrosis Panel regarding appropriate Special Authority criteria.

Discussion

4.5. The Committee noted that funding applications for ivacaftor for the treatment of cystic fibrosis (CF) in patients with the G551D gene mutation have been considered by PHARMAC on a number of occasions. Members noted that in April 2014, the Respiratory Subcommittee deferred making a recommendation on ivacaftor until further clinical trial data became available evaluating ivacaftor in combination with lumacaftor and until PHARMAC had completed further cost utility analysis. The Committee noted that in May 2014 it deferred making a recommendation on ivacaftor for the same reasons. The Committee noted that it reviewed the cost effectiveness of ivacaftor in May 2015 and recommended that the application for ivacaftor be declined based on prohibitive cost and because the clinical trial results for the combination treatment had not yet been published.

4.6. The Committee noted that the application was reviewed by the Rare Disorders Subcommittee in November 2018 and was recommended for funding with a medium priority based on high health need, a lack of disease-modifying treatment options, and moderate quality evidence of a health benefit noting the limited availability of long-term data, subject to Special Authority criteria.

4.7. The Committee noted that PHARMAC had received a number of letters of support from clinicians and members of the public regarding the funding of ivacaftor for CF patients with the G551D mutation. Members acknowledged many of the letters expressed the high health need of people with cystic fibrosis and their families/caregivers, and the high expectations of benefit this treatment may offer. The Committee noted a letter from Cystic Fibrosis New Zealand to PTAC following the Subcommittee recommendation, highlighting the health need of this patient group and expected benefits of treatment with ivacaftor.

4.8. The Committee noted that approximately 4% patients with CF have the Class III (gating) mutation, G551D, on at least one allele, which results in a CFTR protein that is significantly less effective at chloride transport. Members noted that there are additional gating mutations, including G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R, and noted that these are rare and account for approximately 1% of patients with CF. Members noted that in 2017 the FDA approved ivacaftor for 28 additional mutations, suggesting that as many as 14% of patients with CF may benefit from ivacaftor monotherapy.

4.9. The Committee noted that according to the Port CFNZ National data registry 2014, there are 443 patients in New Zealand diagnosed as having cystic fibrosis and of these, 30 have the G551D gene mutation. The cumulative prevalence of cystic fibrosis due to G551D mutation or other Class III (gating) mutations is likely to be less than 1:50,000 and therefore this subgroup of patients with cystic fibrosis could be considered rare.

4.10. Members noted that the Rare Disorders Committee considered that cystic fibrosis overall is not a rare disorder based on the PHARMAC definition, and therefore ivacaftor in combination with other agents, or any other treatments that were approved for use in a wider CF population would not meet PHARMAC's principles for rare disorders and would therefore be considered by PHARMAC through the usual funding assessment process, following Medsafe regulatory approval.

4.11. The Committee considered there was nothing further to add to the Subcommittee's consideration of health need for patients with CF and their family and whānau.

4.12. The Committee noted that new information has been published since it reviewed an application for ivacaftor in 2014, including results of the PERSIST trial (McKone et al. Lancet Respir Med 2014;2:902-10), US and UK data (Bessonova et al., Thorax 2018;0:1-10, Feng et al., Health Aff (Millwood) 2018;37:773-9), as well as a number of studies of ivacaftor in children (Davies JC, et al. Lancet Respir Med. 2016;4:107-15, Rosenfeld et al., Lancet Respir Med. 2018;6:545-53).

4.13. The Committee noted the results of the STRIVE (Ramsey et al NEJM 2011;365:1663-72) and ENVISION (Davies et al. Am J Respir Crit Care Med 2013;187,11:1219-25) Phase III

clinical trials of ivacaftor in patients aged 12 and older, and aged 6-11 years, respectively, that they had reviewed at their meetings in 2014.

4.14. The Committee noted the findings of PERSIST, a phase 3, open-label extension of the STRIVE and ENVISION trials that assessed the safety and efficacy of ivacaftor over 96 weeks in 144 adults and adolescents and 48 children with cystic fibrosis and a G551D-CFTR mutation on at least one allele (McKone et al. 2014). Members noted that most adverse events were mild or moderate and that serious adverse events were reported for 20% of patients during the first 48 weeks and 23% of patients during the subsequent 48 weeks. The Committee noted that two adults and one child discontinued treatment due to adverse events, and two deaths occurred during the study. Members noted that among adolescents/adults and children who previously received ivacaftor, the change in FEV1 at week 96 (after 144 weeks of treatment with ivacaftor) was 9.4 and 10.3 percentage points, respectively and that weight gain reported in the earlier trials was sustained. The absolute increase in weight was 4.1 kg for adolescents/adults and 14.8 kg for children. The Committee noted that the exacerbation rate for patients on placebo was 1.3 per year compared to 0.6 per year after 48 weeks and between 0.8 and 0.9 after between 96 to 144 weeks, with 30% of patients' exacerbation free after 144 weeks. Members noted that data did not indicate the severity of exacerbations, particularly if they were more or less severe than might otherwise be expected.

4.15. The Committee noted the findings of an ongoing observational, post-approval safety study that evaluated the clinical outcomes and disease progression in ivacaftor-treated patients using data from the US and the UK CF registries, which included 1,256 ivacaftor-treated and 6,200 comparator CF patients from the US and 411 ivacaftor-treated and 2,069 comparator CF patients from the UK (Bessonova et al., 2018). Members noted that the average observed treatment length was 2 years in the US and 1.3 years in the UK, and that 74.4% of patients had one copy of G551D in the US compared to 100% in the UK. No new safety concerns were identified. Ivacaftor-treated US patients were observed to have significantly lower risks of death (0.6% vs 1.6%, p=0.011), transplantation (0.2% vs 1.1%, p=0.0017), hospitalisation (27.5% vs 43.1%, p<0.0001) and pulmonary exacerbation (27.8% vs 43.3%, p<0.0001) relative to comparators. Ivacaftor treated patients had reductions in other complications; trends were similar in the UK.

4.16. Members considered that there were several limitations associated with the study published by Bessonova et al. (2018) including the open-label observational study design and that the majority of ivacaftor-treated patients had a class III G551D mutation while the majority of the comparators had a class I/II CFTR genotype. Members considered this raises some questions regarding comparability, although patients with the G551D mutation pre-ivacaftor treatment and comparators had the same rate of exacerbations and FEV1.

4.17. The Committee reviewed results of an observational study that used US claims data to determine the impact of ivacaftor on CF-related hospitalisations by comparing the hospitalisation rate for the 12-month period before and after patients commenced on treatment (Feng et al., 2018). Members noted that 80% of eligible patients with the G551D mutation commenced treatment within a year of FDA approval. The following year, when the label was extended to include patients with other gating mutations, 80% of CF patients that commenced treatment with ivacaftor did not have the G551D mutation. Members noted that all-cause hospital admissions reduced by 55% and CF-related admissions reduced by 81%.

4.18. The Committee noted the results of a 16 week, double-blind, placebo-controlled cross-over, open label study of 36 patients that evaluated the efficacy and safety of ivacaftor in CF patients with a non-G551D gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) (De Boek et al. J Cyst Fibros 2014;13:674-80). Members noted that 8 weeks of ivacaftor resulted in a treatment difference in FEV1 of 10.7 percentage points, and noted that patients also had improvements in body mass index, sweat chloride and respiratory domain score from the Cystic Fibrosis Questionnaire-

Revised. The Committee considered there were no new safety concerns reported in the study.

4.19. Members reviewed the findings of the open-label, single-arm KIWI study which investigated the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children aged 2–5 years with cystic fibrosis and a CFTR gating mutation (Davies JC, et al. Lancet Respir Med. 2016;4:107-15). The Committee noted that ivacaftor 50 mg and 75 mg twice daily appeared to be safe in children over a 24-week period in this study.

4.20. The Committee noted that there is an ongoing Phase 3 clinical trial (ARRIVAL NCT02725567) to assess the safety and efficacy of ivacaftor in children with cystic fibrosis that have the CFTR gating mutation who are under 24 months of age. Members noted that data up to 24 weeks for children aged 12-24 months demonstrated ivacaftor 50 mg and 75 mg twice daily was well tolerated with a safety profile consistent with studies in patients 2 years and older and the authors observed substantial improvements in sweat chloride, a marker of CFTR activity (Rosenfeld et al., Lancet Respir Med. 2018;6:545-53). Ivacaftor showed improvements in markers of pancreatic function and growth parameters were normal at study baseline and generally maintained during treatment. The Committee noted that a trial is ongoing for children aged under 12 months.

4.21. Members agreed with the Subcommittee that clinicians would be likely to treat children under six years of age with ivacaftor if it was available; however, this would currently be an unapproved indication in New Zealand. The Committee noted that 50 mg and 75 mg sachets of ivacaftor granules are available in some countries but are not currently approved by Medsafe or available in New Zealand. The Committee considered that there may be issues with how ivacaftor can be prepared for paediatric use if only film-coated tablets are available, since the tablets are not made to be broken. Members noted that the 75 mg sachets of ivacaftor granules cost the same as the 150 mg tablets in Australia.

4.22. The Committee noted that there was no evidence to support the use of ivacaftor in people with the F508del CTFR mutation (Skilton et al. Cochrane Database Syst Rev. 2019;7:1, Flume P et al. Chest; 2012:142:718-24).

4.23. Members noted the results of two phase 3 clinical trials that assessed the effect of lumacaftor, a CF transmembrane conductance regulator corrector (CFTR), in combination with ivacaftor, a CFTR potentiator, in patients with CF that were homozygous for the F508del CFTR mutation (Wainwright et al. NEJM. 2015; 373:220-31) and reviewed the Cochrane review 2018 regarding Correctors (specific therapies for class II CFTR mutations) for CF (Southern et al. Cochrane Database Syst Rev 2018; 8:CD010966). The Committee noted that there is insufficient evidence that monotherapy provides clinical meaningful benefits in patients with the F508del mutation and noted that combination therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) results in small improvements in clinical outcomes, including FEV1, pulmonary exacerbations and quality of life.

4.24. The Committee noted that the data available regarding the safety and efficacy of ivacaftor available at this time remains limited to three years, with no long-term efficacy and safety data available. Members considered the available evidence suggests that ivacaftor is likely to significantly slow the progression of CF, and lead to reductions in hospital admissions and pulmonary exacerbations. Members considered the data provides a sufficient signal to accept that benefits may be long-lasting and there may be some survival benefit. Members considered that since ivacaftor slows the progression of CF, treatment at a young age would give the greatest benefit. Members noted that improvements in lung function is provided as relative change in FEV compared to baseline and considered that actual FEV results would help inform treatment start times.

4.25. The Committee considered that while ivacaftor may slow the progression of CF, treatment is not curative, and patients are likely to eventually decline. The Committee considered the assumption noted by the Respiratory Subcommittee at its 2014 meeting that the deterioration of CF patients treated with ivacaftor would be similar to that observed in

patients with bronchiectasis, and considered that this assumption is reasonable, though not based on any published evidence. Members considered that the benefit from ivacaftor should be considered over the patient's lifetime in economic modelling.

4.26. The Committee noted the very high proposed cost of ivacaftor and took this into account in its recommendation. Members considered that CF patients have a high health need and there is a lack of disease-modifying treatment CF patients. Members considered that the evidence of a health benefit from treatment with ivacaftor is of good quality and strength (up to 144 weeks), however longer-term evidence is not available.

4.27. The Committee recommended that advice be sought from the Cystic Fibrosis Panel regarding appropriate Special Authority criteria and be provided to PTAC at a future meeting.

5. Agalsidase alfa for the treatment of Fabry Disease

Application

5.1. The Committee reviewed an application for agalsidase alfa for the treatment Fabry disease.

5.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

5.3. The Committee **recommended** that the application to fund agalsidase alfa for the treatment of Fabry disease be **declined** due to low quality evidence consistent with only modest clinically meaningful long-term health benefits.

Discussion

5.4. The Committee noted that the PTAC has previously considered and declined applications for agalsidase alfa and agalsidase beta for the treatment of Fabry disease (PTAC minutes: May 2006, February 2009, November 2011).

5.5. The Committee noted that an application for agalsidase alfa was most recently considered by the Rare Disorders Subcommittee of PTAC in November 2018, at which time the Subcommittee recommended that agalsidase alfa be funded with a medium priority. The Committee noted the Subcommittee made this recommendation based on the high health need of patients with Fabry disease, a lack of alternative treatment options, and low to moderate level of evidence, including evidence of real-world benefit. Members also noted the Subcommittee recommended that PHARMAC consider running a Request for Proposal process for an enzyme replacement therapy (ERT) for the treatment of Fabry disease.

5.6. The Committee noted that Fabry disease is an X-linked lysosomal storage disorder characterised by episodes of pain, angiokeratomas, hypohidrosis, corneal opacity, hearing loss, progressive kidney damage, cardiac disease, and stroke. The Committee considered that the presentation of Fabry disease is highly variable, and that milder forms of the disorder may present only later in life and affect the heart or kidneys.

5.7. The Committee noted that several disease-modifying agents are available for the treatment of Fabry disease including agalsidase alfa, agalsidase beta, and migalastat. The Committee noted that these agents are not funded in New Zealand, and that current management involves best supportive care.

5.8. The Committee reviewed the evidence that was considered by the Rare Disorders Subcommittee, including the retrospective analysis of the international Fabry Outcome Study (Beck et al. Mol Genet Metab Rep. 2015;2:21-7) and the Cochrane Systematic Review of ERT for Fabry disease (El Dib et al. Cochrane Database Syst Rev. 2016;7:CD006663).

5.9. The Committee noted that the study conducted by Beck et al. (2015) was sponsored by Shire and was initiated to collect long-term clinical data for individuals with Fabry disease receiving either agalsidase alfa or no ERT. The Committee noted that the results of an exploratory analysis suggested that less than 10% of treated and untreated patients included in the Fabry Outcome Study could be matched for comparison. The Committee noted that data for patients treated with agalsidase alfa was therefore matched with untreated historical controls from three published sources.

5.10. The Committee noted that in the study conducted by Beck et al. (2015), survival data from the Fabry Outcome Study was compared with survival data from a study conducted by Schiffman et al. (Schiffman et al. Nephrol Dial Transplant. 2009;24:2102-11). The Committee considered that while there was a difference in median survival between the groups (77.5 years for patients receiving agalsidase alfa compared with 60 years for untreated patients), that the Schiffman et al. (2009) population was younger at diagnosis and age of first symptom, which may have been indicative of more severe disease. The Committee further noted that the Schiffman et al. (2009) study included retrospective data from patients with Fabry disease collected from between 1944 and 2002 and considered that the diagnostics and general standard of care for patients with Fabry disease, particularly for cardiac and renal disease, would have improved significantly over that time period, potentially resulting in earlier diagnosis and improved patient outcomes irrespective of ERT.

5.11. The Committee noted that in the study conducted by Beck et al. (2015) the event rate data from the Fabry Outcome Study was compared with morbidity data from a study conducted by Banikazemi et al. (Banikazemi et al. Ann Intern Med. 2007;146:77-86). The Committee noted that the probability of a composite endpoint (first renal, cardiac or stroke event, or death) after 24 months was ~16% in agalsidase alfa-treated patients compared with ~45% in the Banikazemi et al. (2007) untreated cohort. The Committee considered while this indicated that there was a difference in morbidity between the agalsidase alfa treated patients and untreated patients, that differences in the baseline population and methods of data collection made it difficult to compare the data.

5.12. The Committee noted the analysis of renal outcomes in Beck et al. (2015). The Committee considered that the results were difficult to interpret as 20% of males and 12% of females had received angiotensin-converting enzyme inhibitors (ACEI) in the untreated cohort from Schiffman et al. (2009) compared with 57% of males and 65% of females in the Fabry Outcome Study who had received ACEI or angiotensin receptor blockers at some time during the period analysed.

5.13. The Committee noted the analysis of cardiac outcomes in Beck et al. (2015). The Committee noted that patients treated with agalsidase alfa had a negligible annualised rate of change in left ventricular mass indexed to height (LVMI), and that the difference in the rate of change between the treated and untreated cohorts was suggestive of a treatment effect; however, the Committee considered that it was unclear what the long-term clinical significance of stable LVMI was.

5.14. The Committee noted an earlier analysis of data from the Fabry Outcome Study which investigated pain and quality of life after one and two years of treatment with agalsidase alfa (Beck et al. Eur J Clin Invest. 2004;34:838-44). The Subcommittee noted that there was a trend towards a reduction in pain after one and two years of treatment with agalsidase alfa, and that there was a significant small improvement in the quality of life during the first year of treatment that was maintained through the second year of treatment.

5.15. The Committee noted the results of a systematic review of literature regarding quality of life in patients with Fabry disease which found that patients with Fabry disease had significantly worse quality of life compared with the general population, and in contrast to the findings of Beck et al. 2004, that no definite conclusions could be drawn regarding the effect of ERT on quality of life (Arends et al. Orphanet J Rare Dis. 2015;10:77).

5.16. The Committee noted the findings of a systematic review which investigated the efficacy and safety of ERT compared with other interventions, placebo, or no intervention for the treatment of Fabry disease (El Dib et al. Cochrane Database Syst Rev. 2016;7:CD006663). The Committee noted that this publication was an update of the 2010 Cochrane review considered by PTAC in November 2011. Members noted there were three new trials included in the 2016 analysis, including one comparing agalsidase alfa and beta and two exploring different dosing. The Committee noted that El Dib et al. (2016) concluded that the trials comparing ERT with placebo reported a significant improvement with ERT in regard to microvascular endothelial deposits of globotriaosylceramide and in pain-related quality of life; but that the long-term influence of ERT on the risk of morbidity and mortality related to Fabry disease remained to be established, and that there was no evidence demonstrating whether the alfa or beta form was superior.

5.17. The Committee noted the findings of a companion study to El Dib et al. 2016 that involved a linear regression and pooled analysis of proportions from cohort studies identified in the initial systematic review (El Dib et al. PLoS One. 2017;12:e0173358). The Committee considered that there was large variation in results from studies investigating the effect of treatment with agalsidase alfa on renal, cardiovascular, and cerebrovascular complications resulting in a lack of significant difference compared with untreated patients. In contrast, the Committee noted that treatment with agalsidase beta was associated with a significantly lower incidence of renal, cardiovascular, and cerebrovascular complications. The Committee further noted that the rate of all-cause mortality was 10.8% in untreated patients, 9% in agalsidase alfa-treated patients, and 4.4% in agalsidase beta-treated patients; which, whilst not significant, is indicative of a survival benefit with ERT.

5.18. The Committee noted the results of a retrospective cohort study which compared clinical and biochemical outcomes of agalsidase alfa and agalsidase beta for the treatment of Fabry disease in 387 patients from three European Fabry disease centres of excellence (Arends et al. J Med Genet. 2018;55:351-8). The Committee noted that there was no difference in clinical event rate between the ERTs and that there was a more robust decrease in plasma globotriaosylsphingosine and a better reduction in LVMI following treatment with agalsidase beta.

5.19. The Committee considered that the evidence available at this time suggests that agalsidase beta has the same or similar therapeutic effect as agalsidase alfa. The Committee considered that this is supported by retrospective data published following the 2009-2012 shortage of agalsidase beta which indicated that switching to agalsidase alfa or lowering the dose of agalsidase beta was well tolerated and resulted in minimal effects on disease severity (Ghali et al. JIMD Rep. 2012;3:33-43; Pisani et al. Genet Med. 2017;19:275-82).

5.20. The Committee noted that agalsidase alfa is administered every two weeks via intravenous infusion over a period of 40 minutes. Members noted the infusion time is longer with agalsidase beta. The Committee noted that the onset of infusion related reactions generally occurs within the first two to four months after initiation of treatment, and that home-based infusion after this time may be considered for patients who are tolerating the infusions.

5.21. The Committee noted consensus recommendations from the European Fabry Working Group regarding initiation and cessation criteria for ERT in Fabry disease, and considered that aspects of these recommendations could be incorporated into Special Authority criteria, should ERT be funded in New Zealand for the treatment of Fabry disease (Biegstraaten et al. Orphanet J Rare Dis. 2015;10:36).

5.22. The Committee noted the development of JR-051, a biosimilar of agalsidase beta that is currently being investigated in preclinical studies (Morimoto et al. Mol Genet Metab. 2018;125:153-60).

5.23. The Committee noted the Special Authority criteria proposed by the Subcommittee and that further advice would be sought from metabolic clinicians if this application was considered further. Members were unsure regarding initial criterion 3 and renewal criterion 4 regarding

the development of another medical condition that may compromise a response to ERT, noting these criteria were based on the Australian Life Saving Drugs Programme access criteria. The Committee considered the intent of these criteria should be clarified. The Committee noted the extensive set of criteria developed by the European Fabry Working Group included treating asymptomatic classical male patients. Members noted the differences in comparison to the Subcommittee proposed criteria would limit use to symptomatic patients in New Zealand.

5.24. The Committee noted the challenging entry and renewal criteria for Fabry disease and considered that these were comparable to the criteria for funded ERT for Gaucher disease, which is currently managed by a panel. Members considered a similar model could be used for managing funding of ERT for Fabry disease.

5.25. The Committee considered that there was some evidence indicating that treatment with agalsidase alfa improved surrogate markers of disease in patients with Fabry disease, but that this evidence was of low quality and its relevance to long-term outcomes remains unclear. The Committee considered that the evidence regarding the health benefit of ERT was of low quality due to the comparison with historical data, which is unlikely to be directly relevant to the health outcomes of patients with Fabry disease in 2019 due to improvements in diagnostics and medical management over time. The Committee considered that the evidence of a health benefit was not sufficient to recommend funding agalsidase alfa. The Committee noted the high cost of treatment and the possible opportunities regarding a competitive process and reducing the cost of ERT for Fabry disease.

6. Rituximab – Biosimilar for use in multiple indications

Application

6.1. The Committee reviewed an application from Celltrion for CT-P10, a biosimilar of rituximab for use in multiple funded indications.

6.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

6.3. The Committee **recommended** that, subject to Medsafe approval and patent expiry, CT-P10 be listed on the Pharmaceutical Schedule only if cost saving compared with the currently listed rituximab reference product. The Committee considered it would be possible to consider a dual listing of biosimilar rituximab alongside the reference rituximab product with appropriate implementation support to manage this.

6.4. The Committee **recommended** that PHARMAC staff engage with relevant Subcommittees regarding the funding of biosimilar rituximab.

Discussion

6.5. The Committee noted that the application for CT-P10 (Truximab or Ritemvia) requested funding for use in non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis subject to patent expiry, which are the Medsafe approved indications for rituximab. The Committee noted that rituximab is currently funded in New Zealand for these indications, and a number of unapproved indications.

6.6. The Committee noted that six rituximab biosimilars have been approved by the European Medicines Agency (EMA) and that one has been approved by Medsafe (Riximyo). The Committee noted that CT-P10 is currently under review by Medsafe with approval expected in February 2019.

6.7. The Committee noted that the rituximab reference product (Mabthera) has been listed on the Pharmaceutical Schedule since 2005 and has subsidy and delisting protection until 30 June 2019. The Committee noted that there are a number of indication patents that would prevent sole supply of a biosimilar rituximab for the entire market, but that there are several patents expiring in 2019 that provide the opportunity to list a biosimilar rituximab alongside the reference rituximab or to consider sole supply for part of the rituximab market depending on patents. Members noted some indication patents for Mabthera extend to 2026.

6.8. The Committee noted an *in vitro* three-way similarity study which reported that CT-P10, EU-Rituximab, and US-Rituximab were highly similar in terms of physicochemical and biological quality attributes (Lee et al. MAbs. 2018;10:380-96).

6.9. The Committee noted a randomised, double-blind phase 1 study which reported that CT-P10 and the reference rituximab demonstrated equivalent pharmacokinetics, and comparable efficacy, pharmacodynamics, immunogenicity, and safety in 103 patients with rheumatoid arthritis (CT-P10 1.1; Yoo et al. Ann Rheum Dis. 2017; 76:566-70). The Committee also noted that CT-P10 and the reference rituximab demonstrated comparable efficacy and safety at the time of the 72-week follow-up (Yoo et al. BioDrugs. 2017;31:357-67).

6.10. The Committee noted the 56-week open-label extension of the phase 1 studies published by Yoo et al (2017) which reported comparable efficacy and safety in the 20 patients who switched from reference rituximab to CT-P10 and in the 38 patients who continued on CT-P10 (CT-P10 1.3; Park et al. BioDrugs. 2017;31:369-77). The Committee considered that the adverse event profile reported in this study indicates that there should be minimal safety issues associated with changing from reference rituximab to CT-P10.

6.11. The Committee noted that the primary evidence for the therapeutic equivalence of CT-P10 is provided by three randomised controlled phase 3 trials, one conducted in individuals with rheumatoid arthritis (CT-P10 3.2), one conducted in individuals with advanced follicular lymphoma (CT-P10 3.3), and one conducted in individuals with low-tumour burden follicular lymphoma (CT-P10 3.4).

6.12. The Committee noted the randomised, double-blind, phase 3 CT-P10 3.2 trial which investigated the equivalence of CT-P10 and reference rituximab products (US- or EU-sourced) in 372 patients with rheumatoid arthritis (Park et al. MAbs. 2018;10:934-43). The Committee noted that the trial was divided into two parts: part 1 evaluated the pharmacokinetic equivalence after two infusions, and part 2 evaluated efficacy, pharmacodynamics, and safety over 24 weeks. The Committee noted that the study reported that the pharmacokinetic endpoints and primary efficacy endpoint (DAS28-CRP) fell within the predefined equivalence margins; and that the pharmacodynamic, immunogenicity, and safety profiles were similar for CT-P10 and the reference rituximab products.

6.13. The Committee noted the randomised, double-blind, phase 3 CT-P10 3.3 trial which investigated the non-inferior efficacy and pharmacokinetic equivalence of CT-P10 compared with US-sourced reference rituximab in 140 patients with newly diagnosed advanced-stage follicular lymphoma (Kim et al. Lancet Haematol. 2017;4:e362-e373). The Committee noted that a higher proportion of patients randomised to receive CT-P10 had stage IV disease (70% vs 49%) and bone marrow involvement at screening (64% vs 47%) and that patients randomised to CT-P10 had higher median B-cell counts (93 cells per microlitre vs 62 cells per microlitre). The Committee noted that the study reported that the overall response was 97.0% in the CT-P10 group and 92.6% in the reference rituximab group (4.3%; one-sided 97.5% CI -4.25), and that the pharmacokinetic endpoints fell within the predefined bioequivalence margin. The Committee noted that the most common drug-related adverse event was neutropenia (21% CT-P10 vs 7% reference rituximab) and considered that the elevated rate in the CT-P10 arm could be attributable to the differences in baseline characteristics noted above.

6.14. The Committee noted the randomised, double-blind, phase 3 CT-P10 3.4 trial which investigated the therapeutic equivalence of CT-P10 and US-sourced reference rituximab in 258 patients with newly diagnosed low-tumour burden follicular lymphoma (Ogura et al. Lancet Haematol. 2018;5:e543-e553). The Committee noted that the study reported that CT-P10 was therapeutically equivalent to reference rituximab, and that CT-P10 was well tolerated. The Committee noted the authors claim that their study was a sensitive model for assessing biosimilarity of CT-P10 and reference rituximab due to the uniform disease characteristics of low-tumour burden follicular lymphoma and the use of monotherapy.

6.15. The Committee noted CT-P10 is supplied in the same strengths and presentations as the reference product. Members noted the rituximab is regularly compounded into an infusion solution and extended stability information for CT-P10 is available.

6.16. The Committee noted a comment by the authors of Ogura et al. (2018) which suggested that overall response is a more realistic endpoint than survival in biosimilar trials, as the assessment of survival requires a very large number of patients and long-term follow-up.

6.17. The Committee noted the supplier's data regarding market share of CT-P10 in international markets and considered that if this data were accurate that there are likely tens of thousands of patients receiving CT-P10 in other countries, and that no safety concerns have been reported to date.

6.18. Members considered that the evidence provided was in low-risk oncology indications, but that CT-P10 may be used in higher-risk cancers; however, it was noted that there has been no reports of increased mortality in markets where CT-P10 has a large market share (e.g. Netherlands, United Kingdom, and Austria).

6.19. The Committee considered that the evidence available to date supports the bioequivalence and therapeutic equivalence of CT-P10 compared with reference rituximab; however, the Committee noted that CT-P10 is still under consideration by Medsafe.

6.20. The Committee considered that successful implementation of a change to a biosimilar product will require health care providers (HCPs) to be well informed and confident regarding biosimilar data, as the way information is communicated to patients by their HCP can have a significant impact on patient confidence in a biosimilar product.

6.21. The Committee considered that if CT-P10 were to be funded, that it would need to be dual listed with the rituximab reference product for separate indications depending on patent expiry. The Committee considered that PHARMAC would need to develop implementation strategies to support this approach and manage issues related to both a biosimilar and reference product being listed and used for different patient groups.

6.22. The Committee noted the range of factors that can influence the successful introduction of biosimilars, including factors that directly relate to prescriber and patient acceptance. Members noted that rituximab is a hospital-based infusion administered with varied frequency depending on the indication, and that this may help minimise the challenges with biosimilar acceptance, including the nocebo effect.

6.23. The Committee considered it would be possible to consider a dual listing of biosimilar rituximab alongside the reference rituximab product with appropriate implementation support to manage this. Members noted this could provide significant opportunity to reduce costs and consider widening access for current and new indications.

7. Lanreotide acetate and octreotide LAR for the treatment of non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

Application

7.1. The Committee reviewed an application for lanreotide acetate for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs).

7.2. The Committee also reconsidered the evidence for octreotide long-acting release (LAR) for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional GEP-NETs.

7.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.4. The Committee **recommended** that lanreotide acetate be funded with a **low priority** for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs), subject to the following Special Authority criteria:

> Special Authority for Subsidy – Retail Pharmacy
> Initial application – (non-functional neuroendocrine tumour) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
>
> 1. Patient has been diagnosed with unresectable locally advanced or metastatic non-functional gastroenteropancreatic neuroendocrine tumour (GEP-NET); and
> 2. Patient has a grade 1 or 2 tumour (Ki-67 of less than 10%); and
> 3. Patient has a WHO performance status of 0-2; and
> 4. Radiologically confirmed disease progression; and
> 5. Treatment is to be administered in 28 day treatment cycles at a maximum of 120 mg per cycle; and
> 6. Lanreotide acetate to be discontinued at disease progression.
>
> Renewal – (non-functional neuroendocrine tumour) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
>
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment.

7.5. The Committee **recommended** that octreotide long-acting release (LAR) be funded with a **low priority** for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs), subject to the same criteria noted in paragraph 7.4

7.6. The Committee **recommended** that in the event that either lanreotide acetate or octreotide LAR were to be funded for non-functional NETs, that the other agent should only be progressed for funding if cost-neutral or better to the funded agent.

Discussion

7.7. The Committee noted that about half of all NETs are gastroenteropancreatic in origin. The Committee noted that survival for patients with NETs varies depending on the primary site and grade of tumour and that average survival for patients with GEP-NETs is between 9 and 12 years.

7.8. The Committee noted that the initial management approach for patients diagnosed with unresectable locally advanced or metastatic non-functional NETs is watchful waiting.

7.9. The Committee noted that further treatment is warranted once disease progression occurs with currently funded treatment options for patients with locally advanced or metastatic NETs in New Zealand including surgery and ablation for debulking, and chemotherapy (e.g. temozolomide, capecitabine). The Committee noted that octreotide LAR is the only funded for the control of symptoms of functional-NETs.

7.10. The Committee noted that the Cancer Treatment Subcommittee of PTAC (CaTSoP) reviewed the application for lanreotide acetate for the treatment of GEP-NETs in September 2018, and recommended funding the agent with a low priority.

7.11. The Committee noted that the CaTSoP also considered that the sum of the evidence available to date supports the use of long-acting somatostatin analogues for the treatment of non-functional NETs, and considered that lanreotide acetate and octreotide long-acting release (LAR) were likely to provide a similar level of benefit in this indication; the CaTSoP were therefore supportive of widening access to octreotide LAR if cost-effectiveness analysis favoured this agent over lanreotide acetate.

7.12. The Committee noted that an application for octreotide LAR for the treatment of non-functional small intestinal NETs was previously deferred by PTAC in February 2013 and subsequently declined by CaTSoP in March 2013 as while there was a statistically significant effect on progression-free survival, there was a lack of evidence demonstrating a benefit in overall survival or health-related quality of life.

7.13. The Committee noted that somatostatin analogues are widely recognised as being effective at alleviating symptoms associated with functional NETs, and that octreotide LAR is currently funded for the treatment of functional NETs.

7.14. The Committee noted PTAC had previously considered funding of lanreotide acetate for the treatment of functional neuroendocrine tumours (NETs) in 2004 and recommended funding only if cost-neutral or better to octreotide LAR on the basis that these agents had the same or similar therapeutic effect in this setting.

7.15. The Committee noted that the supplier of lanreotide acetate had recently provided an updated submission for its use specifically in unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional GEP-NETs supported by evidence from the randomised, double-blind, placebo-controlled phase 3 CLARINET study.

7.16. The Committee noted that in the CLARINET study 204 patients with advanced non-functioning NETs were randomly assigned to receive 120 mg lanreotide acetate (as an extended-release aqueous-gel formulation) or placebo once every 28 days for 96 weeks (Caplin et al. N Engl J Med. 2014;371:224-33).

7.17. The Committee noted that eligible patients had well-differentiated or moderately differentiated NETs (proliferation scores Ki67 <10% and tumour grades based on the WHO 2010 classification) originating from the pancreas, midgut, hindgut or from an unknown source.

7.18. The Committee noted that 96% of patients enrolled in CLARINET had no tumour progression in the three to six months before randomisation, and that there was a high rate of withdrawal during the study.

7.19. The Committee noted that patients in the placebo arm who had disease progression and patients in the lanreotide arm who had stable disease were eligible to receive lanreotide in the CLARINET open-label extension (OLE) study.

7.20. The Committee noted that in CLARINET the median progress-free survival (PFS) was not reached in the lanreotide acetate arm compared with 18.0 months in the placebo arm (HR 0.47; 95% CI 0.30 to 0.73; *P*<0.001).

7.21. The Committee noted that there was no significant difference in overall survival (OS) between the treatment arms in CLARINET. The Committee considered that other investigations have demonstrated that there is an association between improved PFS and OS for patients with advanced NETs (Strosberg et al. N Engl J Med. 2017;376:125-35; Ter-Minassian et al. Oncologist. 2017;22:165-72). The Committee considered that this association between PFS and OS is specific to the natural history of advanced GEP-NETs, and the lack of association observed in CLARINET was likely due to trial design allowing crossover from the placebo group to the lanreotide acetate group and uncertainty regarding treatments received after progression.

7.22. The Committee considered that there appeared to be no difference in OS between patients who received placebo and patients who received lanreotide acetate in CLARINET from 24 months until the conclusion of CLARINET OLE. The Committee considered that this indicated there was no disadvantage to delaying treatment with lanreotide acetate, and that lanreotide acetate could be initiated effectively after disease progression has occurred.

7.23. The Committee noted that there were no significant differences in quality of life between the treatment arms in CLARINET.

7.24. The Committee noted that 88 patients from CLARINET were enrolled in the CLARINET OLE study; 41 patients continued on lanreotide, and 47 patients crossed over from the placebo arm (Caplin et al. Endocr Relat Cancer. 2016;23:191-9). The Committee noted that the median PFS for patients originally randomised to lanreotide was 32.8 months in CLARINET OLE compared with 18.0 months in CLARINET for patients who received placebo.

7.25. The Committee noted that patients who progressed on placebo in CLARINET who switched to lanreotide acetate in CLARINET OLE had a median time to subsequent progression of 14.0 months. The Committee considered that this indicates that, if it were funded, the median time patients would receive lanreotide acetate would be 14 months, noting that the mean treatment duration may be longer due to a small proportion of patients experiencing an extended progression-free period.

7.26. The Committee noted the results of the PROMID study, a double-blind phase 3b study in which 85 patients with well-differentiated metastatic midgut NETs (functional and non-functional) were randomly assigned to receive octreotide LAR 30 mg or placebo until progression or death (Rinke et al. J Clin Oncol. 2009;27:4656-63). The Committee noted that the median PFS was 14.3 months in the octreotide LAR arm and 6 months in the placebo arm (HR 0.34; 95% CI 0.20 to 0.59; *P* = 0.000072) and that median OS was not estimable in the octreotide LAR arm and 73.7 months in the placebo arm (HR 0.81; 95% CI 0.30 to 2.18; *P* = 0.77).

7.27. The Committee agreed with the conclusion made by CaTSoP that the sum of the evidence available for long-acting somatostatin analogues supports the use of either lanreotide acetate or octreotide LAR for the treatment non-functional NETs and considered that these agents can be considered to provide the same or similar clinical outcome in the treatment of non-functional NETs.

8. Carfilzomib for the treatment of relapsed or refractory multiple myeloma

Application

8.1. The Committee reviewed the application for carfilzomib for the treatment of relapsed or refractory multiple myeloma.

8.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Committee **recommended** that carfilzomib for the treatment of relapsed or refractory multiple myeloma be listed with a **low priority**, subject to the following Special Authority criteria:

Initial application – (relapsed/refractory multiple myeloma)

All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Either:
   - 2.1. Carfilzomib to be used as second line treatment for multiple myeloma; or
   - 2.2. Both;
     - 2.2.1. Carfilzomib to be used as third line treatment for multiple myeloma; and
     - 2.2.2. The patient has experienced severe (grade 3 or higher), dose limiting adverse events with either bortezomib, lenalidomide or thalidomide that precludes further treatment with either of these treatments; and
3. Carfilzomib to be administered in combination with dexamethasone; and
4. Patient has a creatinine clearance of greater than 30 mL/min; and
5. Patient is not refractory to treatment with bortezomib or lenalidomide.

8.4. The Committee considered the ENDEAVOR trial data provided good quality evidence and showed PFS and OS improvement in the carfilzomib group, however, the potential benefit of carfilzomib to New Zealand patients is unclear. The Committee considered that if carfilzomib were to be funded, it would add another option into the sequence of therapies for MM, but given the current dosing schedule, it would significantly impact DHB infusion services and could potentially increase inequities in access.

8.5. The Committee noted there were a large number of currently unfunded new treatments for relapsed or refractory multiple myeloma being researched that have uncertain effectiveness and very high cost, especially when used in combination. The Committee supported CaTSoPs view that wider consultation with relevant clinicians on a preferred national treatment algorithm should be undertaken to better understand the clinical priorities for relapsed or refractory multiple myeloma. The Committee considered the outcome of that consultation should be reviewed by CaTSoP at a future meeting.

Discussion

8.6. The Committee noted that multiple myeloma (MM) is a fatal neoplastic plasma cell disorder characterised by proliferation of malignant plasma cells in the bone marrow, accompanied by secretion of monoclonal immunoglobulins. Multiple myeloma is a relapsing disease characterised by shorter intervals of remission between each subsequent relapse. The Committee noted that UK data shows 5 and 10-year overall survival of patients with MM is ~50% and ~30%, respectively, with treatment, however, the duration of overall survival for New Zealand patients may be less (Hock et al. Intern Med J. 2018 Nov 8. doi: 10.1111/imj.14155).

8.7. The Committee noted that the majority of cases of MM are diagnosed in adults over 44 years of age and that the median age at diagnosis is 70 years. The Committee noted that MM has a higher incidence in Māori (7.6 per 100,000) than in non-Māori (4.9 per 100,000), and a high incidence in Pacific peoples (9.8 per 100,000).

8.8. The Committee noted that MM is treated with sequential lines of therapy and that the proportion of patients who proceed to treatment and the efficacy of treatments generally decreases with each subsequent line of therapy (Yong et al. Br J Haematol. 2016;175:252-64). The Committee noted that treatment for MM may include autologous stem cell transplant (ASCT) which can be incorporated into the initial therapeutic regimen or at relapse, depending on patient eligibility. The Committee noted that the disease may not respond to treatment or patients may progress during treatment ("refractory MM").

8.9. The Committee noted that there are several agents and many multi-drug combinations that are being used internationally to treat MM that are not currently funded in New Zealand, such as daratumumab which is being considered concurrently at this PTAC meeting.

8.10. The Committee noted that agents which are funded in New Zealand for the treatment of MM are bortezomib (a first-generation proteasome inhibitor which is generally administered subcutaneously weekly), and the oral immunomodulatory agents lenalidomide and thalidomide. The Committee noted that New Zealand patients with MM usually receive bortezomib in combination with cyclophosphamide and dexamethasone (CyBorD) as a first-line treatment, followed by thalidomide as second-line treatment (although some will receive bortezomib or lenalidomide as second-line treatment) and the majority of patients receive third-line treatment with lenalidomide.

8.11. The Committee noted that carfilzomib is a second-generation proteasome inhibitor which binds selectively and irreversibly to the active sites of the 20S proteasome of malignant plasma cells, resulting in delayed proliferation and cell death. The Committee noted that carfilzomib is administered as six intravenous infusions per 28-day treatment cycle.

8.12. The Committee noted that the supplier has proposed that carfilzomib be used for the second or third-line treatment of relapsed or refractory MM. The Committee noted that carfilzomib is in the same class as bortezomib, which is funded for first-line treatment of MM and second-line treatment of relapsed or refractory MM in those who have not previously received bortezomib. The Committee considered that the need for the group of patients in this application is similar to the need of patients with MM who receive other agents for relapsed or refractory MM.

8.13. The Committee noted that the key clinical evidence to support the application for carfilzomib comes from the randomised, open-label, phase 3 ENDEAVOR trial, which investigated the clinical benefit of carfilzomib plus dexamethasone compared with bortezomib plus dexamethasone in 929 patients with relapsed or refractory MM who had previously received between one and three prior lines of treatment for MM (Dimopoulos et al. Lancet Oncol. 2016;17:27-38).

8.14. The Committee noted that 54% of the ENDEAVOR trial population were previously treated with bortezomib and that participant characteristics were well balanced between the two treatment groups.

8.15. The Committee considered the open-label design of the ENDEAVOR trial was appropriate due to the different consolidation treatment schedules for carfilzomib (twice-weekly) and bortezomib (once-weekly).

8.16. The Committee noted the results of the first interim analysis of the primary endpoint of the ENDEAVOR trial which was conducted in November 2014 after median follow-up of 11.9 months in the carfilzomib group vs 11.1 months in the bortezomib group. The ENDEAVOR trial interim analysis showed progression-free survival (PFS) of 18.7 months in the carfilzomib group compared to 9.4 months in the bortezomib group (HR 0.53; 95% CI, 0.44 to 0.65; P<0.0001) (Dimopoulos et al. Lancet Oncol. 2016;17:27-38). The Committee noted these results were consistent with a subgroup analysis assessing the impact of prior treatment in 195 ENDEAVOR trial patients who had received one prior line of bortezomib, which showed median PFS of 18.7 months in the carfilzomib group compared to 8.7 months in the bortezomib group (Moreau et al. Leukemia. 2017;31:115-22).

8.17. The Committee noted the results of the subgroup analysis performed during the first interim analysis of the ENDEAVOR trial and considered that the patients who received the least progression-free survival benefit from treatment with carfilzomib were those with creatinine clearance of less than 30 mL/min, those with disease refractory to bortezomib or lenalidomide, and those with missing cytogenetic risk data.

8.18. The Committee noted the results of the second interim analysis of the ENDEAVOR trial which was conducted in January 2017 after median follow-up of 37.5 months in the carfilzomib group vs 36.9 months in the bortezomib group. The ENDEAVOR trial second interim analysis showed median overall survival (OS) of 47.6 months in the carfilzomib group compared with 40.0 months in the bortezomib group (HR 0.791; 95% CI 0.648 to 0.964; one-sided P=0.010) (Dimopoulos et al. Lancet Oncol. 2017;18:1327-37), however, the Committee considered there may be some bias in the overall survival curve due to censoring.

8.19. The Committee noted that a retrospective cohort study (Hock et al. Intern Med J. 2018) suggests the New Zealand patient population with MM may have shorter median OS than the bortezomib group in the ENDEAVOR trial (median OS 40.0 months) and this may influence the potential health benefit of carfilzomib. The Committee considered it was unclear whether any difference in OS was due to characteristics of the New Zealand patient population with MM or due to differences in access to therapeutic agents for MM.

8.20. The Committee noted that Serious Adverse Events (SAEs) occurred in 59% of patients in the carfilzomib group in the ENDEAVOR trial second interim analysis compared with 40% of patients in the bortezomib group. The Committee noted that the most frequently reported grade 3 or worse adverse events in the ENDEAVOR trial were anaemia (16% of patients in the carfilzomib group vs 10% of patients in the bortezomib group) and hypertension (15% vs 3%).

8.21. The Committee noted that the ENDEAVOR trial Clinical Study Report dated November 2017 showed the incidence of peripheral neuropathy (a known toxicity associated with bortezomib) was lower in patients who received carfilzomib, with grade 2 or worse peripheral neuropathy occurring in 6.9% of patients in the carfilzomib group compared with 34.9% in the bortezomib group (P<0.0001).

8.22. The Committee noted the incidence of cardiac failure (a grouped term including multiple types of cardiac toxicity) in the ENDEAVOR trial second interim analysis was higher in the carfilzomib group (5%) than in the bortezomib group (~1%). The Committee also noted that the 2016 ENDEAVOR trial publication reported results of a pre-planned sub-study in 151 ENDEAVOR trial patients which assessed left ventricular ejection fraction (LVEF) reduction, in which 4 patients had significant LVEF reduction during the trial which resolved back to normal on follow-up in all but one patient.

8.23. The Committee noted the results of the third interim analysis of the ENDEAVOR trial (data cut-off July 2017 after at least three years of patient follow up), providing updated OS, safety and subgroup analysis data (Orlowski et al. J Clin Oncol. 2018; 36 (suppl15): abstract 8032) which was consistent with results of the two prior ENDEAVOR trial analyses. The Committee considered the ENDEAVOR trial data provided good quality evidence and that no further OS data would be reported.

8.24. The Committee considered that carfilzomib would be suitable for second-line treatment if a patient has received first-line bortezomib, or as a third-line treatment if a patient has received second-line bortezomib and had experienced severe, dose-limiting adverse events with other agents precluding their further use.

8.25. The Committee considered that if carfilzomib were to be funded, it would add another option into the sequence of therapies for MM rather than displacing or replacing other agents due to the sequential therapeutic approach for this disease. The Committee considered that the supplier estimate of patient numbers was insufficient and that approximately 200 patients would receive carfilzomib in the second-line setting, incorporating all patients who would otherwise receive second-line bortezomib and the majority of patients who would otherwise receive second-line thalidomide for relapsed or refractory MM.

8.26. The Committee considered that if carfilzomib were to be funded it would increase infusion service resource use and could increase inequity due to its treatment schedule which requires more frequent hospital visits for intravenous infusions.

8.27. The Committee considered the ENDEAVOR trial data provided good quality evidence and showed PFS and OS improvements in the carfilzomib group, however, the potential benefit of carfilzomib to New Zealand patients is unclear because the control arm of the trial may have better overall survival rates than New Zealand patients with MM. The Committee considered that if carfilzomib were to be funded, it would add another option into the sequence of therapies for MM (rather than replacing or displacing other agents), would lead to reduced uptake and duration of later lines of therapy (due to the pattern of disease relapse), increase infusion resource usage due to additional intravenous treatment of carfilzomib, and potentially could increase inequity through access to treatment.

8.28. The Committee noted there were a large number of currently unfunded new treatments for relapsed or refractory multiple myeloma being researched that have uncertain effectiveness and very high cost, especially when used in combination. The Committee supported CaTSoPs view that wider consultation with relevant clinicians on a preferred national treatment algorithm should be undertaken to better understand the clinical priorities for relapsed or refractory multiple myeloma. The Committee considered the outcome of that consultation should be reviewed by CaTSoP at a future meeting.

9. Daratumumab for the treatment of relapsed or refractory multiple myeloma

Application

9.1. The Committee reviewed the application from Janssen for daratumumab in combination with bortezomib and dexamethasone for the second-line treatment of relapsed/refractory multiple myeloma.

9.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

9.3. The Committee **recommended** that daratumumab in combination with bortezomib and dexamethasone for the second-line treatment of relapsed/refractory multiple myeloma be deferred until overall survival data from relevant clinical trials becomes available.

9.4. The Committee **recommended** that the application be referred to CaTSoP when further overall survival data is submitted.

Discussion

9.5. The Committee noted that a funding application for daratumumab in combination with bortezomib and dexamethasone for the treatment of patients with relapsed/refractory myeloma had been previously considered by CaTSoP at their meeting in April 2018 and correspondence from the supplier was reviewed by PTAC at their meeting in August 2018. The Committee noted that CaTSoP had recommended that a decision be deferred until longer follow-up data became available and that PTAC had agreed with the Subcommittee's recommendation.

9.6. The Committee noted that multiple myeloma (MM) is a fatal neoplastic plasma cell disorder characterised by proliferation of malignant plasma cells in the bone marrow, accompanied by secretion of monoclonal immunoglobulins. Multiple myeloma is a relapsing disease characterised by shorter intervals of remission between each subsequent relapse. The Committee noted that UK data shows 5 and 10-year overall survival of patients with MM is ~50% and ~30%, respectively, with treatment, however, the duration of overall survival for New Zealand patients may be less (Hock et al. Intern Med J. 2018; Nov 8. doi: 10.1111/imj.14155).

9.7. The Committee noted that the majority of cases of MM are diagnosed in adults over 44 years of age and that the median age at diagnosis is 70 years. The Committee noted that MM has a higher incidence in Māori (7.6 per 100,000) than in non-Māori (4.9 per 100,000), and a high incidence in Pacific peoples (9.8 per 100,000).

9.8. The Committee noted that MM is treated with sequential lines of therapy and that the proportion of patients who proceed to treatment and the efficacy of treatments generally decreases with each subsequent line of therapy (Yong et al. Br J Haematol. 2016;175:252-64). The Committee noted that treatment for MM may include autologous stem cell transplant (ASCT) which can be incorporated into the initial therapeutic regimen or at relapse, depending on patient eligibility. The Committee noted that the disease may not respond to treatment or patients may progress during treatment ("refractory MM").

9.9. The Committee noted that there are several agents and many multi-drug combinations that are being used internationally to treat MM that are not currently funded in New Zealand, such as carfilzomib which is being considered concurrently at this PTAC meeting.

9.10. The Committee noted that agents which are funded in New Zealand for the treatment of MM are bortezomib (a first-generation proteasome inhibitor which is generally administered subcutaneously weekly), and the oral immunomodulatory agents lenalidomide and thalidomide. The Committee noted that New Zealand patients with MM usually receive bortezomib in combination with cyclophosphamide and dexamethasone as a first-line treatment, followed by thalidomide as second-line treatment (although some will receive bortezomib or lenalidomide as second-line treatment) and the majority of patients receive third-line treatment with lenalidomide.

9.11. The Committee noted that daratumumab is a humanised monoclonal antibody that binds to CD38, which is overexpressed in a number of haematological malignancies, including multiple myeloma tumour cells. Members noted that daratumumab inhibits the growth of CD38-expressing cells through multiple mechanisms, including direct killing of tumour cells, modulation of CD38 enzymatic activity and direct and indirect immune-mediated effects.

9.12. Members reviewed the treatment paradigm proposed by the supplier and noted that daratumumab is approved by Medsafe in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

9.13. The Committee noted that the recommended dose of daratumumab is 16 mg/kg body weight administered as an intravenous infusion and noted when used in combination with bortezomib and dexamethasone, daratumumab is given weekly for a total of 9 doses (weeks 1-9), every three weeks for a total of 5 doses (weeks 10-24) and then once every 4 weeks there-after until disease progression. Members noted that the slow infusion rates for daratumumab would require significant infusion times that would significantly impact DHB infusion services.

9.14. Members noted that CaTSoP had previously reviewed the results of the CASTOR (Palumbo et al. N Engl J Med. 2016;375:754-66) and POLLUX (Dimopoulos et al. N Engl J Med. 2016;375:1319-31) trials that provided the primary evidence for the health benefits of daratumumab for the treatment of relapsed/refractory myeloma in the earlier submission.

9.15. The Committee reviewed the results of the longer-term follow up data from the CASTOR (Spencer et al. Haematologica. 2018;103: 2079-87) and POLLUX (Dimopoulos et al. Haematologica 2018;103:2088-96) trials, which assessed the safety and efficacy of daratumumab in in combination with bortezomib and dexamethasone, or lenalidomide and dexamethasone, respectively.

9.16. The Committee noted that the medium follow-up from the CASTOR trial was 19.4 months and that the medium PFS was 16.7 months for the daratumumab treatment arm (daratumumab in combination with bortezomib and dexamethasone) vs 7.1 months for the

control (bortezomib and dexamethasone) (HR 0.39, p<0.0001). The Committee noted that the overall response rate was 83.8% in the daratumumab treatment group compared to 63.2% in the control group (p<0.001) and noted that 11.6% of patients treated with daratumumab had no detectable minimal residual disease compared 2.4% of patients in the control group. Members noted that there was significant cross-over in the study, with 64 patients in the control group opting for daratumumab treatment following progression. Members noted that the latest publication states that overall survival data remained immature and further follow up is planned. The Committee considered that significant crossover may prevent assessment of observable differences in OS.

9.17. The Committee noted the results of exploratory post hoc secondary analysis performed in the publication and noted that daratumumab in combination with bortezomib/dexamethasone was superior to bortezomib/dexamethasone alone in subgroups based on prior treatment exposure (bortezomib, thalidomide, or lenalidomide), lenalidomide-refractory status, time since last therapy (≤12, >12, ≤6, or >6 months), or cytogenetic risk. Members noted that the greatest benefit in PFS was observed in patients that were treated with daratumumab following the first relapse.

9.18. The Committee noted that there were no significant differences in quality of life data from the CASTOR trial. Members considered this means it is unlikely more detail will be published on this analysis. The Committee noted that safety data was similar to what has been reported previously, there were no differences in the number of trial discontinuations and noted that patients treated with daratumumab were more likely to diagnosed with a second malignancy compared to the control group.

9.19. Members noted that the medium follow-up from the POLLUX trial was 25.4 months and that the medium PFS was not reached in daratumumab treatment arm (daratumumab in combination with lenalidomide with dexamethasone) vs 17.5 months for the control arm (lenalidomide with dexamethasone) (HR 0.41, p<0.0001). The Committee noted that the overall response rate was 92.9% in the daratumumab treatment group compared to 76.4% in the control group (p<0.001). Members noted that there was no OS data reported although considered that the lower rates of crossover in POLLUX compared to CASTOR may mean that obtaining overall survival data should be possible.

9.20. The Committee noted the results of exploratory post hoc secondary analysis performed in the publication and noted that daratumumab in combination with dexamethasone/lenalidomide was superior to dexamethasone/lenalidomide alone in subgroups based on prior treatment exposure (thalidomide, or lenalidomide), bortezomib-refractory status (all P<0.01). Members noted that the greatest benefit in PFS was observed in patients that were treated with daratumumab following the first relapse.

9.21. The Committee noted that the quality of life data from the POLLUX trial slightly favoured treatment with daratumumab. The Committee noted that safety data was similar to what has been reported previously, there were no differences in the number of trial discontinuations or diagnosis with a second malignancy compared to the control group.

9.22. Members reviewed the results of an indirect comparison meta-analysis of randomised controlled trials of monoclonal antibodies versus histone deacetylase inhibitors in combination with bortezomib or lenalidomide plus dexamethasone for the treatment of relapsed or refractory multiple myeloma (Zheng et al. J Immunol Res. 2018;7646913) as well as a metanalysis of 24 trials of different relapsed/refractory multiple myeloma treatment regimens (Luo et al. Cancer Manag Res. 2018;10:2817-23). The Committee noted that the results from Luo et al (2018) demonstrated that daratumumab in combination with lenalidomide and dexamethasone resulted in the best efficacy in terms of PFS, but daratumumab was not included in the analysis for overall survival since this data has not yet been reported.

9.23. The Committee also reviewed a publication of the cost-effectiveness of daratumumab-based triplet therapies in patients with relapsed or refractory multiple myeloma (Zhang et

al. Clin Ther. 2018;40:1122-39) and noted that the addition of daratumumab to either bortezomib and dexamethasone or lenalidomide and dexamethasone was not cost effective under the US pricing system.

9.24. Members noted that PBAC did not recommend the listing of daratumumab for use in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone in relapsed or refractory multiple myeloma due to the very high and uncertain incremental cost-effectiveness ratios, and a preference to have both combinations of therapies available for patients. Members noted that PBAC considered the comparators used in the trial evidence to be reasonable for the economic analysis but highlighted that other comparators, such as bortezomib and cyclophosphamide, would have also been appropriate. The Committee noted that PBAC also noted that at the time of review, both trials were yet to reach a median PFS in their intervention arm or median OS in either arm making the magnitude of incremental benefit uncertain.

9.25. Members noted that an economic evaluation for daratumumab in combination with bortezomib or lenalidomide for relapsed/refractory multiple myeloma has not been conducted by NICE or SMC. The Committee noted that daratumumab is recommended for fourth line use in the UK and Scotland.

9.26. The Committee considered that while the longer-term follow up data looked promising for PFS and minimal residual disease, the data is still too immature for overall survival data to be reported.

9.27. The Committee recommended that daratumumab in combination with bortezomib and dexamethasone for the second-line treatment of relapsed/refractory multiple myeloma be deferred until overall survival data from relevant clinical trials become available. The Committee recommended that the application be referred to CaTSoP when further overall survival data is submitted.

10. Sofosbuvir/ velpatasvir/ voxilaprevir for the treatment of chronic hepatitis C

Application

10.1. The Committee reviewed the application for sofosbuvir/ velpatasvir/ voxilaprevir for the treatment of chronic hepatitis C.

10.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Committee **recommended** that Sofosbuvir/ velpatasvir/ voxilaprevir be listed with a **medium priority** subject to the prescription being written by a gastroenterologist and who have been treated with a direct acting antiviral and did not achieve Sustained Virologic Response (SVR) and has evidence of Resistance associated variants (RAVs).

Discussion

10.4. The Committee noted that from 1 July 2016, PHARMAC funded ledipasvir with sofosbuvir (Harvoni); paritaprevir, ritonavir and ombitasvir with dasabuvir (Viekira Pak); and paritaprevir, ritonavir and ombitasvir with dasabuvir and ribavirin (Viekira Pak-RBV).

10.5. The Committee noted that paritaprevir, ritonavir and ombitasvir with dasabuvir with or without ribavirin (Viekira Pak +/- RBV) is open listed, but considered that it is in practice only suitable for patients with genotype 1 infection who do not have decompensated cirrhosis. Ledipasvir with sofosbuvir (Harvoni) is funded for patients with HCV who have severe liver disease.

10.6. The Committee noted that on 1 February 2019, PHARMAC funded glecaprevir with pibrentasvir (Maviret) without restrictions, and that this listing coincided with the delisting of paritaprevir, ritonavir and ombitasvir with dasabuvir with or without ribavirin (Viekira Pak +/- RBV).

10.7. The Committee noted that as a result of direct acting antiviral agent (DAA) listings since February 2019 there are treatment options for all treatment-naive chronic hepatitis C patients regardless of genotype or liver disease status. Members also considered that as patients are treated there are those that do not achieve sustained virologic response (SVR). The observed rates of patients failing to achieve SVR following treatment with Viekira Pak +/- ribavirin in New Zealand is approximately 4%. Members considered that the supplier's estimate of 10% SVR failure was an overestimation.

10.8. The Committee noted that this application sought to fund sofosbuvir/ velpatasvir/ voxilaprevir for patients who have received a DAA regimen but who have not achieved an SVR. Members considered that in order to distinguish virologic failures from non-virologic failures, all patients who have not achieved SVR with DAA treatment should have formal NS5A resistance testing performed to confirm Resistance associated Variants (RAVs) are present.

10.9. The Committee noted that the observed rate of patients not achieving SVR who also had RAVs was approximately 3% (approximately 75% of SVR failures from DAA treatment have RAVs). Members considered that the current unmet health need, as a result of DAA therapy, not achieving SVR and with the presence of RAVs was approximately a cohort of 90 patients. The Committee noted that the ongoing rate of patients not achieving SVR and possessing RAVs with glecaprevir with pibrentasvir was lower than that for Viekira Pak and that it would likely contribute to the cohort at a rate of 0.5 – 1.0% of the treated group.

10.10. The Committee noted that sofosbuvir, velpatasvir and voxilaprevir is a fixed dose oral tablet containing 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir (28 tablets per pack). The recommended dose is one tablet, taken once daily with food. The duration of treatment is 12 weeks for all adults with or without compensated cirrhosis.

10.11. The Committee considered the primary pivotal evidence is provided by the POLARIS 1 and POLARIS 4 Phase 3 RCTs described in Bourlière et al. N Engl J Med. 2017; 376:2134-46. Members noted that in active treatment arms 96% and 98% of patients treated with Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi) achieved SVR in POLARIS 1 and 4 respectively. Members noted in POLARIS 4 that in the comparator arm, sofosbuvir with velpatasvir, 90% of patients achieved SVR. Members noted that reported adverse reactions were minimal.

10.12. Members considered that the resulting chronic hepatitis C patient group with a current unmet health need are patients that have not achieved sustained virologic response with funded or imported direct acting antivirals and who have RAVs.

10.13. The Committee noted that patients who failed to achieve SVR with Viekira Pak but who did not have RAVs, could be retreated with glecaprevir with pibrentasvir (Maviret). Members considered that for patients that have not achieved SVR and possess RAVs the MAGELLAN-3 Study (NCT02939989) has shown promising results. Patients in this study received Maviret with sofosbuvir and ribavirin for 12 weeks, or 16 weeks if they are genotype 3. This may be a potential alternative to Sofosbuvir/ velpatasvir/ voxilaprevir.

10.14. The Committee considered that Harvoni, which is currently funded for patients with severe liver disease, regardless of the genotype is less effective in genotype 3 patients. Members considered that sofosbuvir with velpatasvir (Epclusa) which has been considered by this committee and recommended with a medium priority should be funded in place of Harvoni as it is more effective in this genotype.

10.15. In conclusion, the Committee considered that there was high quality evidence that Vosevi (Sofosbuvir/ velpatasvir/ voxilaprevir) was effective at providing a sustained virological response in patients where another direct antiviral treatment had previously failed, and that this group had a high health need, but noted its high cost.

11. Review of antidiabetic agents for the treatment of Type 2 diabetes

Application

11.1. The Committee considered the currently available data for cardiovascular risks and benefits of DPP4i, GLP1 and SGLT2i in the treatment of type 2 diabetes mellitus (T2DM) and whether this data indicated a class effect.

Recommendation

11.2. The Committee **recommended** that advice be sought from the Diabetes Subcommittee regarding the appropriate place of SGLT2i inhibitors and GLP-1 agonists in the New Zealand treatment paradigm, further consideration of class effect with these agents including the impact of trial population heterogeneity on reported outcomes, and appropriate access criteria including definition of high risk cardiovascular populations.

Discussion

11.3. The Committee noted that the health need of patients with T2DM has been well documented in previous PTAC and subcommittee minutes. The Committee considered that it was well-established that T2DM places a significant burden on the New Zealand Health system, and particularly Pasifika, Māori and South Asian populations. In these groups T2DM is more prevalent, more severe, and generally has an earlier onset of disease.

11.4. The Committee noted that the New Zealand treatment paradigm differs from the European and American treatment paradigms where a range of oral antidiabetic agents from all classes (SGLT2i, DPP4 and GLP1) are generally used in combination prior to commencing insulin.

11.5. The Committee noted that the NZ Diabetes Guidelines published in 2011 appeared not to have been updated to reflect the new evidence available for the long-term efficacy of antidiabetic agents.

11.6. The Committee noted the joint consensus report for the Management of hyperglycaemia in T2DM published in 2018 by the American Diabetes Association (ADA) and the European Association for the study of diabetes (EASD) (Davies et al, Diabetes Care. 2018;41:2669-701).

11.7. The Committee noted that the report recommended that:

- T2DM with established atherosclerotic CVD should be prescribed an SGLT2i or GLP-1 receptor agonist with proven cardiovascular benefit;
- T2DM with atherosclerotic cardiovascular disease with heart failure or heart failure risk be prescribed an SGLT2i;
- T2DM with chronic kidney disease irrespective of cardiovascular disease risk should be prescribed an SGLT2i which has been shown to reduce the progression of chronic kidney disease; if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce the progression of chronic kidney disease should be prescribed

11.8. The Committee noted that this appeared to reflect a shift in the diabetes treatment paradigm from a focus on solely good glycaemic control to consideration of improved patient outcomes, including cardiovascular and renal outcomes, and quality of life.

11.9. The Committee noted that applications for antidiabetic agents have been reviewed by PTAC and the Diabetes Subcommittee individually and together on a number of occasions.

11.10. The Committee noted that the three classes of antidiabetic agents work to reduce hypoglycaemia by different mechanisms of action:

- Sodium-glucose cotransporter 2 inhibitors (SGLT2i), limits glucose absorption in the kidneys, increasing the amount of glucose that is expelled in the urine and reducing the amount of glucose present in the blood;
- Glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonists) mimic the hormone incretin;
- Gliptins (DPP-4 inhibitors) prevent the action of DPP-4, an enzyme that degrades the hormone incretin.

11.11. The Committee noted that overall antidiabetic agents were generally similar in the treatment of T2DM in terms of reducing glycated haemoglobin (HbA1c) by approximately 0.5% to 1% when added to metformin.

11.12. The Committee noted that until recently there has been a lack of evidence supporting clinically significant benefits other than a decrease in HbA1c.

11.13. The Committee noted that clinical trials with longer duration follow-up were conducted for antidiabetic agents following the Food and Drug Administration (FDA) release of a Guidance for Industry in 2008 detailing that all new anti-diabetic agents were required to demonstrate they do not increase the risk of long-term microvascular complications in addition to demonstrating improvements in surrogate markers like HbA1c.

11.14. The Committee noted that there are a large number of cardiovascular outcome trials for antidiabetic agents. The Committee noted that some have already reported data but a number of studies are ongoing with data expected to be published in the near future.

11.15. The Committee noted it had previously individually considered cardiovascular outcome data for empagliflozin, exenatide and liraglutide and that the supplier of dapagliflozin had provided recently published cardiovascular outcome data for this agent which was also being specifically considered at this meeting.

Evidence

11.16. The Committee noted the long-term trial evidence for antidiabetic agents and cardiovascular outcome data available to date including:

- Canagliflozin: CANVAS and CANVAS R Neal et al, N Engl J Med. 2017;377:644-57
- Dapagliflozin: DECLARE-TIMI 58 – Wiviott et al, N Engl J Med. 2019;380:347-57
- Empagliflozin: EMPA-REG outcome – Zinman et al, N Engl J Med. 2015;373:2117-28
- Liraglutide: LEADER trial – Maso et al, N Engl J Med. 2016;375:311-22.
- Semaglutide: SUSTAIN 6 – Maso et al, N Engl J Med. 2016;375:1834-44

- Exenatide: EXSCEL – Holman et al, N Engl J Med. 2017;377:1228-39.
- Albiglutide: HARMONY – Hernandez et al, Lancet. 2018;392:1519-29.

11.17. The Committee also considered additional evidence from various publications, systematic reviews and meta-analyses of antidiabetic agents including those detailed below.

11.18. The Committee noted a systematic review and meta-analysis of SGLT2i which included 34 RCTs of SGLT1i and 9,154 patients. The Committee noted the results from DECLARE-TIMI where not included in this analysis and noted the authors considered the evidence quality used for the meta-analysis, to be of low quality due to study variability and publication bias (Storgaard et al. PLoS One. 2016;11:e0166125).

11.19. The Committee noted a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in T2DM which identified 3 trials with 34,322 patients, 60.2% with established cardiovascular disease. The study reported a reduction in major adverse cardiac events (MACE) with SGLT2i compared to placebo of 11% (HR 0.89, 95%CI 0.83–0.96). Sub-analysis demonstrated the reduction in MACE was statistically significant in patients with atherosclerotic cardiovascular disease (HR 0.86, 95%CI 0.80-0.93) but the difference was not statistically significant for patients without atherosclerotic cardiovascular disease (HR 1.00, 95%CI 0.87-1.16) (*P* for interaction 0.0501) (Zelniker TA et al. Lancet 2019;393:31-9).

11.20. The Committee noted that the risk of cardiovascular death or hospitalisation for heart failure was lower with SGLT2i compared to placebo (HR 0.77, 95%CI 0.71-0.84) as was the risk of progression for renal disease (HR0.55, 95%CI 0.48-0.64). The risk of cardiovascular death, hospitalisation for heart failure and progression for renal disease was similar regardless of atherosclerotic cardiovascular disease status.

11.21. The Committee noted that magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in hospitalisations for heart failure (p for interaction 0.0073) and lesser reductions in the progression of renal disease (p for interaction 0.0258) in patients with more severe kidney disease at baseline.

11.22. The Committee considered that Zelniker et al, 2019 demonstrated SGLT2i have moderate benefit on the occurrence of MACE and that the benefit is greatest in a population of T2DM with established cardiovascular disease. However, there is a reduction in heart failure hospitalisation and progression of renal disease with SGLT2i regardless of existing atherosclerotic cardiovascular disease or history of heart failure.

11.23. The Committee noted the real world CVD-REAL 2 Study, which compared the initiation of SGLT2i with other glucose-lowering agents, 27% of patients had established CVD. The authors concluded SGLT2i initiation resulted in statistically significant reductions in the risk of death, heart failure hospitalisation, death or heart failure hospitalisation, myocardial infarction and stroke compared to other glucose-lowering agents (Kosiborod et al. Diabetes Obes Metab. 2018;20:1983-7).

11.24. The Committee noted a real world study of 28,408 Swedish patients initiating therapy with dapagliflozin or other glucose-lowering drugs over the three-year period 2013 to 2016 (Norhammar A, et al Diabetes Obes Metab. 2019 doi: 10.1111); and that 34% of the study population had established cardiovascular disease. The Committee noted that the study reported dapagliflozin demonstrated a statistically significant reduction in hospitalisation for heart failure or CVD mortality combined, hospitalisation for heart failure alone and CVD mortality alone when compared to other glucose-lowering drugs. The Committee noted that the occurrence of MACE, myocardial infarction or stroke did not differ between the two study arms.

11.25. The Committee noted a publication by Birkeland et al 2018 which aimed to investigate how representative the trial populations of four pivotal SGLTi cardiovascular outcome trials were

to a general population of T2DM (Birkeland KI, et al. Diabetes Obes Metab. 2018. doi: 10.1111/d). The Committee noted that the authors concluded the proportions of the population with prevalent CVD was lower in the general population than in the cardiovascular outcome trials and that the average age was higher; and compared to the general population, the DECLARE-TIMI trial had the highest representativeness (59%) followed by CANVAS (34%), EMPA-REG (21%) and VERTIS-CV (17%).

11.26. The Committee noted a cumulative review including 15 cardiovascular outcome studies of glucose-lowering agents including the latest 3 to be published. The Committee noted that the review suggested that with respect to GLP-1 receptor agonists the agents were similar; and that with regard to SGLT2i although the DECLARE trial of dapagliflozin demonstrated a protective effect on the risk heart failure in T2DM patients with CVD, the reduction in MACE was not comparable in magnitude to the MACE reductions demonstrate by empagliflozin and canagliflozin (Home et al, Diabetologia. 2019; 62:357-69).

11.27. The Committee noted a network meta-analysis which reported that SGLT2i and GLP-1 receptor agonists reduce MACE and all-cause mortality as compared to placebo and SGLT2i reduce all-cause mortality compared to GLP-1 receptor agonists (OR 0.76, 95%CI 0.61-0.94). In contrast, DPP-4 inhibitors were reported not to reduce MACE or mortality when compared to placebo and higher all-cause mortality when compared to SGLT-2 inhibitors (OR 1.53, 95%CI 1.24-1.89) and GLP-1 receptor agonists (OR 1.16, 95%CI 1.01-1.33) (Fei et al, Int J Cardiol. 2018;254:291-6)

11.28. The Committee noted a review of renal outcomes (Muskiet et al, Lancet Diabetes Endocrinol. 2018;6:674-6).

General comments

11.29. The Committee considered that the evidence for cardiovascular and renal outcomes with antidiabetic agents was evolving and overall there could be some bias in the published literature for cardiovascular outcome trials as earlier clinical trials stopped after non-inferiority of the primary outcome was achieved limiting the ability to observe a positive impact on cardiovascular outcomes.

11.30. The Committee considered that based on currently available data overall the various DPP4 agents appeared to have the same or similar effect and are safe within the glucose-lowering algorithm but have neither positive or negative cardiovascular effects. The Committee considered that cardiovascular outcome trials for DPP4i appear to have highlighted a safety risk of pancreatitis.

11.31. The Committee considered that GLP1 trials show cardioprotective effect with respect to mortality, with positive effects for all agents in this class observed throughout the study duration which was indicative of a class effect from these agents. The Committee considered that evidence indicates GLP1 could provide benefit for a wider patient population than just those with established CVD. Members considered that given the relatively early beneficial effect on already damaged arteries observed in trial populations use at a younger age may improve outcomes. The Committee considered that, as GLP1s were administered by injection, patients may prefer to use oral agents instead.

11.32. The Committee considered that based on published literature to date SGLT2i appear to have some benefits in reduction of hospital admission for heart failure and slowing progression of composite renal outcomes, with some showing a reduction in cardiovascular mortality, however the evidence of cardiovascular benefit is in patients with established heart disease only. The Committee considered that SGLT2i likely provided the greatest benefit of the three antidiabetic agent classes for patients with or at high risk of heart failure.

11.33. The Committee considered that currently published longer term follow up data for newer antidiabetic agents do not yet show definitively the renal benefit for patients with renal

disease, however SGLT2i likely provide benefit for patients with progressive decline in eGFR.

11.34. The Committee noted that, while dapagliflozin data indicates benefits in terms of reducing hospitalisations for heart failure and progression of renal decline regardless of existing atherosclerotic CVD or a history of heart failure (Zelniker et al. Lancet 2019;393:31-9) the findings for MACE outcomes are not concordant with the empagliflozin and canagliflozin studies. The Committee considered that it was unclear the reason for these differences but heterogeneity between trials may be a contributing factor.

11.35. The Committee considered that while the literature appeared to be unresolved as to similarity of outcomes from the various newer antidiabetic agents, members considered it was likely each of these classes of agents had the same or similar within class therapeutic effects as indicated by real world studies.

11.36. The Committee noted that from the available analyses, the absolute risk reductions from SGLT2i over 5 years for hospitalisation for heart failure are estimated to be about 0.8% and for renal disease progression 1.4% in patients with multiple risk factors. The Committee noted this would mean that to prevent 1 event over 5 years compared with placebo numbers needed to treat would be 124 for hospitalisation for heart failure and 73 for renal disease progression (Verma et al Lancet 2019; 393:3-5).

11.37. The Committee considered that based on currently published evidence, the New Zealand population to gain the greatest benefit from antidiabetic agents would likely be patients who had not achieved glycaemic control on maximum doses of metformin and/or a sulphonylurea.

12. Dapagliflozin for the treatment of type 2 diabetes

Application

12.1. The Committee considered the funding of dapagliflozin in light of recently published data for the impact of dapagliflozin on cardiovascular outcomes in type 2 diabetes from the DECLARE–TIMI 58 trial.

Recommendation

12.2. The Committee **recommended** that dapagliflozin be funded with **medium priority** for the treatment of patients with type two diabetes and high cardiovascular risk, noting the importance of appropriately defining this population.

12.3. The Committee **recommended** that advice be sought from the Diabetes Subcommittee regarding appropriate access criteria, including definition of a high cardiovascular risk population.

Discussion

12.4. The Committee noted that the health need of patients with T2DM has been well documented in previous PTAC and subcommittee minutes. The Committee considered that it was well-established that T2DM places a significant burden on the New Zealand Health system, and particularly Pasifika, Māori and South Asian populations. In these groups T2DM is more prevalent, more severe, and generally has an earlier onset of disease.

12.5. The Committee noted that applications for antidiabetic agents have been reviewed by PTAC and the Diabetes Subcommittee individually and together on a number of occasions.

12.6. The Committee noted that overall antidiabetic agents were generally similar in the treatment of T2DM in terms of reducing glycated haemoglobin (HbA1c) by approximately 0.5% to 1% when added to metformin.

12.7. The Committee noted that until recently there has been a lack of evidence supporting clinically significant benefits other than decreased HbA1c (which is but an intermediate outcome).

12.8. The Committee noted it had previously considered cardiovascular outcome data for empagliflozin, exenatide and liraglutide; and the supplier of dapagliflozin has now provided recently published cardiovascular outcome data for this agent.

12.9. The Committee noted that the cardiovascular risks and benefits of the newer antidiabetic agents for the treatment of type 2 diabetes were also being reviewed at this meeting including whether these were class effects.

Evidence

12.10. The Committee noted the randomised, double-blinded, phase three cardiovascular outcome trial for dapagliflozin, DECLARE-TIMI (Wiviott et al, N Engl J Med 2019;380:347-57) of 17,160 patients with T2DM (10,186 did not have atherosclerotic cardiovascular disease). Patients were randomised 1:1 to receive dapagliflozin 10mg daily or placebo and were followed for a median of 4.2 years.

12.11. The Committee noted that the primary efficacy outcome measure was major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, or ischaemic stroke) and a composite of cardiovascular death or hospitalisation for heart failure.

12.12. The Committee noted that DECLARE-TIMI demonstrated non-inferiority of dapagliflozin compared to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], <1.3; P<0.001 for noninferiority) but did not result in a lower rate of MACE [8.8% dapagliflozin vs 9.4 placebo; hazard ratio (HR) 0.93, 95% CI 0.84–1.03].

12.13. The Committee noted that dapagliflozin did result in a statistically significant reduction in the rate of death or hospitalisation for heart failure compared to placebo (4.9% dapagliflozin vs. 5.8% placebo; HR 0.83, 95%CI 0.73 to 0.95) which reflected a lower rate of hospitalisation for heart failure (2.5% dapagliflozin vs 3.3% placebo; HR 0.73, 95%CI 0.61−0.88).

12.14. The Committee noted that there was no statistically significant difference between dapagliflozin and placebo for death from any cause (HR 0.93, 95%CI 0.82−1.04), death from cardiovascular disease (HR 0.98, 95%CI 0.82−1.17), occurrence of fatal or non-fatal myocardial infarction (HR 0.89, 95%CI 0.77-1.01) or the occurrence of fatal or non-fatal stroke (HR 1.01, 95%CI 0.84-1.21).

12.15. The Committee noted dapagliflozin demonstrated a statistically significant reduction in renal events (4.3% dapagliflozin vs 5.6% placebo; HR, 0.76, 95%CI 0.67 to 0.87).

12.16. The Committee noted that the occurrence of diabetic ketoacidosis was greater with dapagliflozin than with placebo (0.3% vs. 0.1%, *P* = 0.02), as was the rate of genital infections that led to treatment discontinuation or were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001).

General Comments

12.17. The Committee considered that evidence from DECLARE demonstrated a moderate benefit from dapagliflozin in terms of reduced hospital admission for heart failure and slowing progression of renal disease, and for patients with established cardiovascular disease a reduction in MACE and all-cause mortality. However, the reduction in HbA1c remained in the 0.5-1% range as with other antidiabetic agents.

12.18. The Committee noted that, while dapagliflozin data indicates benefits in terms of reducing hospitalisations for heart failure and progression of renal decline regardless of existing atherosclerotic cardiovascular disease or a history of heart failure (Zelniker et al. Lancet 2019;393:31-9) the findings for MACE outcomes are not concordant with the empagliflozin and canagliflozin studies. The Committee considered that it was unclear the reason for these differences but heterogeneity between trials may be a contributing factor.

12.19. The Committee considered that currently available evidence indicated dapagliflozin would provide greater benefit to patients with T2DM with established atherosclerotic cardiovascular disease and T2DM patients at risk of developing renal disease or heart failure.

13. Meningococcal B vaccine for the prevention of meningitis

Application

13.1. The Subcommittee reviewed the application from GSK Ltd for the meningococcal B vaccine, 4CMenB (Bexsero), for universal childhood vaccination on the Pharmaceutical Schedule.

13.2. The committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

13.3. The Committee **recommended** that 4CMenB be listed in the Pharmaceutical Schedule for universal childhood vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a **medium priority.**

13.4. The Committee **recommended** that 4CMenB be listed in the Pharmaceutical Schedule for adolescents in close-living situations with a **medium priority**.

Discussion

13.5. The Committee noted that this application was considered by the Immunisation Subcommittee at its February 2018 meeting. At that meeting, the Immunisation Subcommittee recommended that 4CMenB be listed with a medium priority for both universal infant vaccination and for individuals in close-living situations.

13.6. The Committee noted that there were 105 invasive meningococcal disease (IMD) cases reported in New Zealand in 2017 and 113 cases reported in 2018. Meningococcal serogroup B (Men B) was the predominant group during the period from 2013 to 2016, accounting for 65% of all meningococcal cases. Members noted that while the number of cases of Men B is still high in NZ, there has been increases in Meningococcal strains Y and W.

13.7. The Committee noted that IMD is a rapid onset disease, that can have devastating lifelong consequences; approximately 10% of patients die even with appropriate medical care and up to 20% of survivors have major permanent sequalae including brain damage, adrenal impairment, hearing loss, renal failure and disfigurement. Members noted that meningococcal infection is often misdiagnosed, progressing from non-specific symptoms, such as fever and irritability, to death within 24 hours of onset, even with medical intervention. The Committee considered that rapid progression leaves clinicians with a narrow window for diagnosis and intervention, underscoring the need for disease prevention through immunisation.

13.8. The Committee noted that Men B disease disproportionately affects infants under 1 year of age, and Māori and Pacific Island populations, with Māori and Pacific populations exhibiting four times higher rates of meningococcal B disease across all age groups compared to the non-Māori/non-Pacific population from 2007–2016. Members noted that Māori and Pacific

infants <1 year of age had a six times higher rate of meningococcal B disease from 2007–2016 compared to non-Māori/non-Pacific Island children.

13.9. The Committee noted that 4CMenB is a multicomponent meningococcal group B vaccine containing purified recombinant meningococcal protein antigens consisting of four highly immunogenic components: three recombinant outer membrane proteins (neisserial heparin binding antigen [NHBA], neisserial adhesin A [NadA], and factor H binding protein [fHbp]) and outer membrane vesicles derived from *N. meningitidis* group B strain NZ98/254.

13.10. The Committee considered that there is no direct evidence from randomised controlled trials that 4CMenB vaccination reduces rates of invasive meningococcal disease. The Committee noted there may be some potential for cross-strain protection against non-B serogroups with 4CMenB, as the antigens it contains are proteins that could be present on the surface of any meningococci rather than the type-specific polysaccharide capsule. However, the Committee considered that any potential health benefit arising from the potential cross-strain protection should not be included in any assessment without robust evidence to support it.

13.11. The Committee considered a Phase IIb, open-label, randomised trial that investigated the immunogenicity and reactogenicity of 4CMenB with or without routine infant vaccines (Gossger et al. JAMA. 2012;307:573-82). The Committee noted that between 51% – 61% of infants developed a fever of ≥38.0°C after 4CMenB and routine vaccines were administered together, compared with 23% – 36% when routine vaccines were administered alone. The Committee noted that in the United Kingdom it is recommended that infants receive three doses of paracetamol following 4CMenB vaccination.

13.12. The Committee noted the combined publication of two multicentre, Phase III, primary and booster studies that investigated the immunogenicity and safety of 4CMenB administered concomitantly with routine vaccines (Vesikari T, et al. Lancet 2013;381:825-35). The Subcommittee noted that 4CMenB was immunogenic, that there was no clinically relevant interference with routine vaccines, and that reactogenicity increased when 4CMenB was given with routine vaccinations.

13.13. The Committee considered a phase IIIb, open label, multicentre, extension study that evaluated long term antibody persistence and booster responses in children aged 35 months to 12 years who received different dose schedules (2+1, 3+1 or 2+0 catch-up schedule). (Martinon-Torres et al. J Infect. 2018;76:258-69). The Committee noted that antibody persistence, booster responses and safety profiles were similar with either 2+1 or 3+1 dose schedules.

13.14. The Committee considered a systematic review and meta-analysis randomised trials that compared the immunogenicity or safety of 4CMenB with the originator meningococcal B recombinant vaccine or routine vaccines in children or adolescents (Flacco et al. Lancet Infect Dis. 2018;18:461-72). The review included 10 randomised trials and eight follow-on extension trials. The Committee noted that 30 day seroconversion rates were high, ranging from 84% to 92% depending on the strain, declining by six months but increasing again to higher than 93% for all strains after a booster dose. Immunogenicity remained high 6 months after the booster dose for all for strains in adolescents (≥77%) and against two strains in children (5/99 and 44/76-SL ≥67%). In children, the immunogenicity returned to pre-booster levels for strains 44/76-SL (62%) and NZ98/254 (35%). The Committee noted that the incidence of acute serious adverse reactions was 5.4 per 1000 individuals, compared to 1.2 per 1000 for routine vaccines. The main serious adverse events noted were febrile convulsions, arthritis and Kawasaki disease. Moderate effects were fever (24%) and injection site pain (74%).

13.15. The Committee considered a national observational cohort study of 4CMenB vaccination that was introduced to infants as part of a publicly funded national immunisation programme in England (Parikh et al. Lancet. 2016;388:2775-82). The Committee noted that vaccine

coverage was 92.1% with vaccine effectiveness of 82.9% and noted that there was a 50% incidence rate ratio (IRR) reduction in Men B cases compared with the pre-vaccine period.

13.16. The Committee considered a study assessing the coverage of meningococcal strains by 4CMenB for isolates obtained during 2007-08 and 2014-15 in England and Wales, using the Meningococcal Antigen Typing System (MATS) (Parikh et al. Lancet Infect Dis. 2017;17:754-62). The Committee noted that proportion of meningococcal group B isolates predicted to be covered by 4CMenB was 73% in 2007-08 but reduced to 66% in 2014-15. The Committee noted that MATS typing is not yet available in New Zealand so the predicted coverage of strains circulating in New Zealand is unknown.

13.17. The Committee considered a systematic literature review on *N. meningitidis* IMD sequelae and HRQoL in survivors of all ages and their caregivers in high income countries from 2001 to 2016. (Olbrich et al. Infect Dis Ther. 2018;7:421-38). The review included 31 studies, mostly of childhood IMD cases, in which physical, neurological and psychological sequelae were identified. The Committee noted that a high proportion of IMD survivors are affected by a range of sequelae and HRQoL reduction persisting for years after infection. Children had higher rates of sequelae and more severe sequelae compared to adults. HRQoL was also reduced in patients' families and caregivers over the long term. Members considered a follow-up study of family members of meningitis survivors with and without long-term sequelae used the EQ-5D to assess health status after 12 years; the overall utility value for survivors with sequelae was 0.78 compared to 0.97 for survivors without sequelae. The family reported health status of survivors with sequelae was lower than for those without sequelae on all dimensions of the EQ-5D (mobility 24% vs 1%, self-care 19% vs 1%, usual activity 37% vs 3%, pain/discomfort 38% vs 4% and anxiety/depression 46% vs 9%) and the overall utility value for survivors with sequelae on the EQ-5D was 0.78 compared with 0.97 for survivors with no sequelae. The Committee considered that the systematic review provided high quality evidence, but noted that there was no New Zealand specific information, point estimates or confidence intervals given in the review.

13.18. The Committee considered that it is reasonable to extrapolate the effectiveness and IRR from England to reflect health benefit in New Zealand but noted that the strain coverage may be different between the two countries. The Committee considered that the strength and quality of the evidence for health benefits that may be gained from 4CMenB were of good strength and quality. Members noted that individuals in closed-living situations (boarding schools, university halls of residence, prison populations) would be at increased risk of infection.

13.19. The Committee considered that Men B is a relatively uncommon condition with a high health need and there is indirect evidence of 4CMenB effectiveness. The Committee noted the high cost of the 4CMenB vaccine and low cost-effectiveness for 4CMenB as part of the National Immunisation Schedule for infants and for close-living populations.

14. Meningococcal ACWY/C vaccine for the prevention of meningitis

Application

14.1. The committee reviewed the application for Meningococcal ACWY/C vaccine for the treatment of meningitis.

14.2. The committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

14.3. The committee **recommended** that meningococcal ACWY vaccine be listed with a **high priority** for adolescents (aged 13-19 years) in close-living situations.

14.4. The committee **recommended** that meningococcal ACWY vaccine be listed with a **low priority** for universal adolescent (aged 13-19 years) vaccination.

14.5. The committee **recommended** that meningococcal ACWY vaccine be listed with a **low priority** for children aged 1 to 4 years.

Discussion

14.6. The Committee noted that 105 cases of meningococcal disease were notified in New Zealand in 2017 and 113 cases were notified in 2018. The Committee noted that meningococcal B (Men B) was the predominant strain in cases from 2013 – 2016, with the proportion of cases due to meningococcal strains ACWY (Men ACWY). In 2018, 55% of cases were for non-B disease, with Group W being the most prevalent of the non-B groups. The Committee noted that in 2017 and 2018, there were more cases of Men W in people 20 years of age and older than those under 20 years of age. The Committee noted that meningococcal infection rates are typically higher in Māori and Pacific people compared with the total population.

14.7. The Committee noted that household crowding is an important risk factor for meningococcal disease, independent of ethnicity and noted that in 2016 the highest age-specific disease rates were among those aged under 1 year (18.6 per 100,000, 11 cases) and 1–4 years (6.9 per 100,000, 17 cases).

14.8. Herd immunity was seen as a key strategy for meningococcal disease control in the UK. Prior to the introduction of MenC vaccination in adolescents and young adults, these age-groups accounted for 25% of carriage rates. A 71% reduction in MenC carriage was seen a year after the vaccine introduction. After just 2 months since the introduction of the Men ACWY adolescent/fresher boosters, a small study has demonstrated a 39% decrease in Men Y carriage and 36.2% decrease in combined CWY carriage in university students (Findlow H et al., Pediatric Drugs 2016;18:83-7).

14.9. The Committee considered a Public Health England report describing a Men C vaccination programme in England (Public Health England 2017; Health Protection Report Volume 11 Number 38) as well as surveillance data from England for laboratory confirmed Men C cases (Findlow et al. Euro Surveill. 2019;24:1700818). The Committee noted that the UK Men C vaccination programme has evolved over time with the introduction of new vaccines and changing disease epidemiology. The Committee noted that the UK had a very low prevalence of Men C with 42 cases 2015, falling to 37 cases in 2016. Between 2011/12 and 2015/16 there was a case fatality rate of 11% and vaccine effectiveness (VE) was between 91 - 96% within 12 months of immunisation for all targeted ages. Members considered that while this data provided little objective information, the report was supportive of the UK Men C vaccination programme.

14.10. The Committee considered a narrative review outlining the implementation of meningococcal vaccination programmes in a number of countries, with a range of meningococcal vaccines (Vuocolo et al. Hum Vaccin Immunother. 2018;14:1203-15). The Committee noted that this was a narrative review describing real-world examples of vaccination strategies to control meningococcal disease with vaccines targeting groups A, B, C and ACWY.

14.11. The Committee considered a systematic review and meta-analysis of the immunogenicity of meningococcal ACWY tetanus toxoid conjugate vaccine (ACWY-TT, Nimenrix) (Pellegrino et al. Pharm Res. 2015;92:31-9). The Committee noted that the systematic review identified 15 randomised controlled trials comparing Men ACWY-TT vaccine to other meningococcal vaccines including meningococcal ACWY diphtheria toxin conjugate vaccine (ACWY-DT, Menactra). The Committee noted that Men ACWY-TT is highly immunogenic with a robust immune response in all age groups. The systematic review included one study comparing Men ACWY-TT to Men ACWY-DT, with 1016 participants aged 10-25 years and concluded that both vaccines gave a similar immune response. The

Committee considered that the systematic review and meta-analysis provided high quality evidence.

14.12. The Committee considered the New Zealand data sheet for Menactra (data sheet). The Committee noted that adverse events of vaccination vary with age. Injection site pain and swelling occur in about 30% and fever in 12%, but rates are lower in children aged 2-10 years and lower again in adolescents and adults.

14.13. The Committee considered a systematic literature review on *N. meningitidis* IMD sequelae and HRQoL in survivors of all ages and their caregivers in high income countries from 2001 to 2016. (Olbrich et al. Infect Dis Ther. 2018;7:421-38). The review included 31 studies, mostly of childhood IMD cases, in which physical, neurological and psychological sequelae were identified. The Committee noted that a high proportion of IMD survivors are affected by a range of sequelae and HRQoL reduction persisting for years after infection. Children had more sequelae and more severe sequelae compared to adults. HRQoL was also reduced in patients' families and caregivers over the long term. A follow-up study of family members of meningitis survivors with and without long-term sequelae used the EQ-5D to assess health status after 12 years. The overall utility value for survivors with sequelae was 0.78 compared to 0.97 for survivors without sequelae. The family reported health status of survivors with sequelae was lower than for those without sequelae on all dimensions of the EQ-5D (mobility 24% vs 1%, self-care 19% vs 1%, usual activity 37% vs 3%, pain/discomfort 38% vs 4% and anxiety/depression 46% vs 9%). The overall utility value for survivors with sequelae on the EQ-5D was 0.78 compared with 0.97 for survivors with no sequelae. The Committee considered that the systematic review provided high quality evidence but noted that there was no New Zealand specific information, point estimates or confidence intervals given in the review. The Committee noted that the systematic review provided high quality evidence regarding the high prevalence of health consequences in terms of mortality, morbidity and the effect of meningococcal disease on family and caregivers.

14.14. The Committee noted that there are two quadrivalent Men ACWY vaccines available in New Zealand (ACWY-D, Menactra and ACWY-TT, Nimenrix). The Committee noted that these are considered equivalent in overseas jurisdictions.

14.15. The Committee noted that more non-group B meningococcal cases occur in people aged 20 years or older but noted that herd immunity from immunising younger age groups is postulated to make the disease less prevalent, although there is little direct evidence to support this. The Committee considered that the indirect evidence is that high vaccination rates lead to sustained lower prevalence and sequelae. Members noted that there was uncertainty regarding the incident rate reduction for New Zealand, which presented an issue for modelling the benefit.

14.16. The Committee agreed with the Immunisation Subcommittee that adolescents in close-living situations (such as university halls of residence, boarding schools) would likely benefit the most from Men ACWY vaccination. Members noted that universal adolescent vaccination in New Zealand would aim to achieve high rates of vaccination to achieve the herd immunity observed in the UK, but there was no direct evidence of benefit. The Committee considered that there was no direct evidence of benefit for universal childhood vaccination.

15. Alprostadil for use in penile Doppler exams

Application

15.1. The Committee reviewed the application to fund alprostadil 10 or 20 mcg for use in penile Doppler exams.

15.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

15.3. The Committee **recommended** that alprostadil be funded for use in penile Doppler exams in hospitals only if cost-neutral to papaverine.

15.4. The Committee considered that there was poor evidence that funding alprostadil 10 or 20 mcg would provide health benefits, because there was poor evidence that the test it supported would provide useful information in the treatment of erectile dysfunction. As such, the Committee recommended alprostadil be funded only if it was no more expensive than already-funded alternatives.

Discussion

15.5. The Committee considered that the evaluation of the application for alprostadil was made difficult due to it having limited clinical information and a lack of clarity on the availability or value of penile Doppler ultrasonography. Members spoke to some radiology departments who stated they would not perform this exam and considered that its use may be regional. Members noted that many physicians would consider CT angiography more appropriate for clinical investigation of undifferentiated arterial erectile dysfunction in the rare event that clinical history and examination were unable to provide meaningful diagnostic information.

15.6. The Committee noted that guidelines for the treatment of erectile dysfunction (Burnett et al. J Urol. 2008;200:633-641) recommend several psychological and behavioural approaches first, then the use of PDE-5 inhibitors such as sildenafil, before penile Doppler examinations are conducted. Because of this, members considered that the group in question is likely to be small.

15.7. The Committee considered that alprostadil would be effective at inducing an erection before the Doppler exam, and that it has a quick onset which is good for use before a procedure.

15.8. Members considered that if the lack of funded alprostadil was a barrier to performing a penile Doppler exam, then funding it could provide a health gain through allowing more testing to be done.

15.9. The Committee noted that the cause of erectile dysfunction is often psychological, and so members questioned how often a Doppler exam would provide information that would aid in treatment. Members also considered that there is a very high false positive rate with this exam. Members considered that because of these two issues, the value of the exam is poor.

15.10. The Committee considered that PDE-5 inhibitors would usually be a solution to the core issue, and that sildenafil is the preferred agent for erectile dysfunction. Members discussed if widening access to sildenafil may be more appropriate than funding alprostadil.

15.11. The Committee discussed whether funding alprostadil 10 or 20 mcg for penile Doppler exams would lead to its use for other indications, such as for erectile dysfunction itself. The Committee considered that it did not know what alprostadil would be used for if funded this way, but considered that alprostadil would not be recommended as a first-line treatment for erectile dysfunction. The Committee considered it would be inappropriate to set funding criteria for alprostadil that required patients to have tried sildenafil, as sildenafil is not currently funded for erectile dysfunction.

15.12. The Committee considered that the spend on alprostadil would be very low, mainly due to low use. Members discussed other alternative treatments and noted that papaverine was listed for use in hospitals without restriction.

15.13. In conclusion, the Committee considered that there was insufficient evidence that funding alprostadil 10 or 20 mcg would provide health benefits, because there was a lack of evidence that the test it supported would provide useful information in the treatment of

erectile dysfunction. As such it recommended that alprostadil be funded only if was no more expensive than already-funded alternatives.