

# **Record of the Pharmacology and Therapeutics Advisory Committee Meeting**

## **Held on 9 & 10 August 2018**

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

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**Present:**

**PTAC members:**

Mark Weatherall (Chair)  
Alan Fraser  
Jane Thomas  
Jennifer Martin (via teleconference 10-8-18)  
Marius Rademaker (Thursday 9-8-18 only)  
Matthew Strother  
Melissa Copland  
Sean Hanna  
Simon Wynn Thomas  
Stuart Dalziel  
Tim Stokes

**1. Subcommittee Minutes**

**Analgesic Subcommittee**

- 1.1. The Committee noted and accepted the record of the Analgesic Subcommittee of PTAC held on 1 March 2018.

**Endocrinology**

- 1.2. The Committee noted and accepted the record of the Endocrinology Subcommittee of PTAC held on 17 May 2018.
- 1.3. The Committee noted that a proposal to widen access to denosumab was on the agenda for this meeting.

**Transplant and Immunosuppressants**

- 1.4. The Committee noted and accepted the record of the Transplant Immunosuppressant Subcommittee of PTAC held on 3 October 2017, including the recommendations to widen access to valganciclovir in transplant populations with high priority as recommended by the Subcommittee.

**Cancer Treatments**

- 1.5. The Committee noted and accepted the record of the Cancer Treatments Subcommittee of PTAC held on 13 April 2018, with the exception of item 8.
- 1.6. In regards to item 8, olaparib for the treatment of BRCA-mutated relapsed ovarian cancer, the Committee requested the application including the results of the SOLO-2 study be reviewed by PTAC at a future meeting.

**2. Correspondence & Matters Arising**

Correspondence re CaTSoP review of daratumumab

- 2.1. The Committee noted that in April 2018, CaTSoP considered an application from Janssen for daratumumab to be used in combination with bortezomib and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma (MM) (minutes item 6.16-6.29).
- 2.2. The Committee noted that CaTSoP recommended that a decision regarding the funding of daratumumab for the treatment of patients with relapsed/refractory MM be deferred until longer-term follow-up data from the relevant clinical trials are made available.

- 2.3. The Committee noted that Janssen's original submission was provided in full to the Subcommittee. It was noted the Subcommittee minute did not detail comments about the conference posters Janssen provided which included updated data from the published interim analyses of the POLLUX and CASTOR trials. These were:
- Weisel et al. Efficacy and safety of daratumumab, bortezomib and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated analysis of CASTOR. Presented at EHA 2017. Madrid, Spain;
  - Lentzschet al. Daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR). Presented at ASCO 2017. Chicago;
  - Dimopoulos et al. Efficacy and safety of daratumumab, lenalidomide, and dexamethasone (DRd) versus Rd alone in relapsed or refractory multiple myeloma (RRMM): updated analysis OS POLLUX. Presented at EHA 2017. Madrid, Spain; and
  - Bahlis et al. Daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (POLLUX). Presented at ASCO 2017. Chicago.
- 2.4. The Committee considered that, in general, conference posters are considered low quality evidence and that the posters provided in this case were insufficient for the Committee to come to a different recommendation to the Subcommittee. The Committee also considered the evidence provided was also insufficient to recommend that CaTSoP consider the matter again at their next meeting.
- 2.5. The Committee noted a concerning international trend to publish interim analyses in peer-reviewed journals and then only provide selected further data as conference proceedings, which, based on the experience of the committee, are likely subject to lower standards of peer-review. The Committee noted posters may be peer-accepted, but not necessarily peer-reviewed in the same way that journal articles are reviewed. The Committee considered that in the absence of further peer-reviewed publications, indexed and searchable Clinical Study Reports may need to be provided to give a more complete picture of the data, methodology and overall study quality.

#### Correspondence re Pembrolizumab for first-line NSCLC

- 2.6. The Committee noted that in March 2017, CaTSoP considered an application for pembrolizumab as a first-line treatment for advanced NSCLC whose tumours express programmed death ligand 1 (PD-L1) at a level of  $\geq 50\%$  and recommended funding with low priority.
- 2.7. The Committee noted that PTAC had considered the funding of pembrolizumab as a first-line treatment for patients with PD-L1 positive advanced NSCLC on several occasions. The Committee noted that PTAC had previously deferred making a recommendation pending PTAC's review of further data from peer-reviewed pre-specified database-lock-related analysis in terms of magnitude and confidence intervals for estimates of survival differences.
- 2.8. The Committee noted that the supplier had since further responded to the issues raised by PTAC regarding the funding of pembrolizumab for the treatment of first-line advanced NSCLC and provided additional information to support the application.
- 2.9. The Committee considered that no new peer-reviewed published information for quality of life or longer-term follow-up of KEYNOTE-024 had been provided.

- 2.10. The Committee considered that the information provided did not address the issues previously raised by PTAC with regards to the application for pembrolizumab as a first-line advanced NSCLC treatment.
- 2.11. The Committee considered that while lower grades of evidence were accepted in support of funding applications, there were limitations in the interpretation and critical appraisal of these forms of evidence. The Committee considered that one of the advantages of peer-reviewed published articles was that these generally included sufficient details of the trial protocol and 'Consort' diagrams; which provide context to the data set and results as a whole.
- 2.12. The Committee considered that the selected and redacted sections of the Clinical Study Report provided gave an incomplete picture of the overall study quality.
- 2.13. The Committee considered that if further peer-reviewed published data was not available then the full unredacted Clinical Study Report would likely be required to address issues of transparency in the trial design and results for KEYNOTE-024. The Committee considered that this would need to be provided as an indexed, searchable PDF file.
- 2.14. The Committee noted that the supplier had recently submitted a funding application to PHARMAC seeking reimbursement of pembrolizumab in combination with pemetrexed and chemotherapy for the first-line treatment of metastatic NSCLC. The Committee considered that the data supporting the combination application may be of relevance for PTAC's consideration of the previous application for pembrolizumab alone as a first-line treatment for NSCLC.

#### Correspondence for Ocrelizumab PTAC Review

- 2.15. The Committee noted that in February 2018 it considered an application from Roche Products for ocrelizumab to be used in primary progressive multiple sclerosis (PPMS). The Committee noted it recommended that the application for ocrelizumab in PPMS be declined.
- 2.16. The Committee noted correspondence received from Roche Products (New Zealand) Limited in April 2018 providing commentary on the decision and the Committee's appraisal of the ORATORIO pivotal trial, as well as a request to redact portions of the minute relating to the appraisal of the evidence. The Committee considered the matters raised in the correspondence and remained confident in its previous decision based on the evidence it considered. The Committee considered that its view remained unchanged in the absence of new evidence.

### **3. Sapropterin for the treatment phenylketonuria in those at risk of cognitive impairment**

#### Application

- 3.1. The Committee reviewed the application for sapropterin for the treatment of hyperphenylalaninaemia (HPA) in individuals with phenylketonuria (PKU) at risk of impaired cognitive development.
- 3.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

#### Recommendation

- 3.3. The Committee **recommended** that sapropterin for the treatment of hyperphenylalaninaemia due to phenylketonuria (PKU) in all individuals with PKU be listed

with a low priority, subject to criteria limiting funding to patients who demonstrate a response to sapropterin.

- 3.4. The Committee reiterated its previous **recommendation** that PHARMAC consider broadening the range of dietary options of PKU supplements available on the Pharmaceutical Schedule.

#### Discussion

- 3.5. The Committee noted that PKU is a metabolic disorder resulting from a deficiency in phenylalanine hydroxylase that results in increased blood and urine concentrations of phenylalanine and its metabolites.
- 3.6. The Committee noted that complete enzyme deficiency results in classic PKU, in which serum phenylalanine concentrations exceed 1200 µmol/L. Residual enzyme activity causes moderate PKU (900-1200 µmol/L), mild PKU (600-900 µmol/L), mild HPA (360-600 µmol/L), and benign HPA not requiring treatment (120-360 µmol/L).
- 3.7. The Committee noted that the incidence of PKU in New Zealand is 1 in 15,000 births per year, and that there are approximately 160 patients known to have PKU in New Zealand.
- 3.8. The Committee noted that a previous application for the use of sapropterin for the treatment of HPA due to PKU or tetrahydrobiopterin (BH4) deficiency was reviewed by PTAC in May 2016. At that time, PTAC recommended that sapropterin be funded for women who are planning to become pregnant, or are pregnant, where dietary phenylalanine restriction has been inadequate, with high priority. They recommended that sapropterin for non-pregnant patients be declined and that sapropterin for the treatment of HPA due to BH4 deficiency be considered on an individual basis via the Named Patient Pharmaceutical Assessment policy ([PTAC minute – 2016-05](#)).
- 3.9. The Committee noted this was a reapplication for sapropterin for a targeted group considered by the applicant to have a greater health need due to the risk of impaired cognitive development. The Committee noted the supplier had provided seven articles as evidence for the efficacy and safety of sapropterin in patients at risk of impaired cognitive development that had not previously been considered by the Committee.
- 3.10. The Committee noted that untreated PKU is characterised by intellectual disability and that cognitive outcome for patients with PKU appears to be closely correlated with phenylalanine levels.
- 3.11. The Committee noted evidence demonstrating that early-treated patients with classical PKU exhibited no generalised learning impairment, but did exhibit impairment in complex executive functions and speed of processing ([Palermo et al. Neuropsychology. 2017;31:255-67](#)).
- 3.12. The Committee noted evidence from the PKU-COBESO study reporting that patients with PKU have phenylalanine-related difficulties with social-cognitive functioning and social skills, and that high levels of phenylalanine during childhood and early adolescence have a greater influence on social-cognitive functioning and social skills later in life than recent phenylalanine-levels ([Jahja et al. J Inherit Metab Dis. 2016;39:355-62](#)). Patients with childhood and lifetime phenylalanine  $\geq 360$  µmol/L had poorer cognitive and mental health outcomes than controls ([Jahja et al. J Inherit Metab Dis. 2017;31:437-47](#)).
- 3.13. The Committee noted that current treatment options for PKU include dietary restriction of phenylalanine and supplementation of other essential amino acids. The Committee noted that there is a high rate of non-compliance with these treatments, particularly for teenage patients, that the available supplements are expensive and unpalatable, and that even with

- good compliance there may be cognitive impairment. Members noted the diet restriction is very challenging for some patients and families, and the reasons for this may be unclear.
- 3.14. The Committee noted that over 50% of patients with PKU dispensed PKU supplements in NZ were under the age of 20 years.
  - 3.15. The Committee noted that sapropterin is a synthetic version of BH4 which increases tolerance to dietary phenylalanine. The Committee noted that the recommended dose of sapropterin is 5-20 mg/kg/day, adjusted to achieve appropriate phenylalanine levels. The Committee noted that this application is for a generic version of sapropterin and there is now potential for competition in this market. Members noted both products available in New Zealand are dispersible tablets.
  - 3.16. The Committee noted that in May 2016, PTAC reviewed a number of publications supporting that sapropterin is effective in lowering blood phenylalanine levels and improving protein tolerance ([PTAC minute – 2016-05](#)). In May 2016, PTAC members noted that, although there are no standard criteria to define responsiveness to sapropterin, a 30% reduction in blood phenylalanine levels is commonly used.
  - 3.17. The Committee noted that applications for the funding of sapropterin have been reviewed by several international health technology assessment agencies. The Committee noted that the PBAC recommended the listing of sapropterin for patients with proven BH4 deficiency in 2012, and deferred a decision regarding the listing of sapropterin for PKU in 2018. Sapropterin is available in the UK for pregnant women with PKU who are unable to establish adequate dietary control of phenylalanine and an application for the treatment of HPA in sapropterin-responsive patients with PKU is currently being reviewed by the Scottish Medicine Consortium.
  - 3.18. The Committee noted the open-label, phase 3b SPARK trial that investigated the efficacy, safety, and pharmacokinetics of 10 mg/kg/day sapropterin in 109 children under 4 years of age with confirmed sapropterin-responsive phenylketonuria ([Muntau, et al. Orphanet J Rare Dis. 2017;12:47](#)). The Committee noted that at Week 26, patients receiving sapropterin plus a phenylalanine-restricted diet had a mean phenylalanine tolerance of 80.6 mg/kg/day compared with 50.1 mg/kg/day in the diet-only group (difference 30.5 mg/kg/day; 95% CI 18.7-42.3;  $P<0.001$ ).
  - 3.19. The Committee noted a clinical study that investigated the long-term effects of sapropterin treatment in nine pre-pubertal patients with HPA ([Tansek et al. J Pediatr Endocrinol Metab. 2016;29:561-6](#)). The Committee noted that the results demonstrated that after 2 years, the daily phenylalanine tolerance tripled from a pre-treatment median value of 620 mg to 2000 mg ( $P<0.001$ ), and that the median blood phenylalanine levels did not change significantly. The Committee noted that all patients in the study had discontinued supplementation with amino acids, with the exception of two patients aged under four years who continued supplementation at one-third of the pre-treatment daily amount.
  - 3.20. The Committee noted a post-hoc analysis of a prospective, non-interventional, observational study that investigated the impact of PKU on the health-related quality of life (HRQoL) of patients and their parents in seven European countries ([Bosch et al. Orphanet J Rare Dis. 2015;10:80](#)). The Committee noted that the results of the PKU-QOL instrument demonstrated that the highest impact scores were for emotional impact of PKU, anxiety about blood phenylalanine levels, and guilt regarding poor adherence to dietary restriction. The Committee also noted that patients receiving sapropterin reported lower practical and emotional impacts of the diet and supplement intake.
  - 3.21. The Committee noted the Key European guidelines for the diagnosis and management of patients with phenylketonuria ([Lancet Diabetes Endocrinol. 2017;5:743-56](#)). The Committee noted that the guidelines recommend a target phenylalanine level of 120-360  $\mu\text{mol/L}$  for all age groups (children up to 12 years [Grade B], patients 12 years and older

[Grade D], and pregnant patients). The Committee noted that the guidelines recommend that all patients with PKU warrant testing for sapropterin responsiveness by genotyping or sapropterin loading. The Committee further noted that the guidelines recommend that treatment with sapropterin should only be prescribed in cases of proven long-term sapropterin-responsiveness, defined as an increase in the amount of natural protein of 100% or more, or improved biochemical control (phenylalanine >75% in target range), and proven by a trial (of up to 6 months) of treatment with sapropterin.

- 3.22. The Committee considered that all patients with PKU are at risk of cognitive decline, and that, based on the reviewed evidence, defining a subpopulation at particular risk was not possible at this time. Therefore, members were supportive of considering funding for the entire PKU population.
- 3.23. The Committee considered that children already exhibiting impaired cognitive development attributable to PKU would still derive benefit from treatment with sapropterin in order to stop further progression, and that these children would therefore be included in the total population at risk.
- 3.24. Members considered that treatment with sapropterin is primarily about providing some flexibility for the strict PKU diet, thereby improving quality of life. Members noted that an increased variety of supplements for PKU may provide a similar improvement in quality of life.
- 3.25. The Committee noted that in May 2016 it considered that it would be preferable to have more funded dietary options with PKU supplements available compared with sapropterin treatment, and that PHARMAC was currently assessing new supplement products. Members noted that some patients with PKU require extensive support to manage the PKU diet and have poor control regardless, and any improvement in the range of products available would be unlikely to provide an additional benefit for these patients. Members noted that some patients would likely stop PKU dietary supplements completely if they responded to sapropterin, while others may continue with reduced supplement requirement.
- 3.26. The Committee considered that PHARMAC should seek advice from the National Metabolic Service in order to gain a comprehensive understanding of patient need and the benefits of sapropterin treatment compared with additional PKU supplement options. The Committee considered that input from patient advocacy groups should also be sought.
- 3.27. The Committee considered the new evidence provided suggested sapropterin may provide benefit to patients, particularly for those who struggle to manage the restrictive PKU diet; however, it would be difficult to restrict to specific patients and to quantify expected benefits. The Committee considered all patients with PKU should be able to access sapropterin in addition to using dietary supplements to optimise control of phenylalanine levels. Members considered the National Metabolic Service should have input into developing Special Authority criteria for sapropterin.

#### **4. Denosumab widening access in the treatment osteoporosis**

##### Application

- 4.1. The Committee reviewed the application for widening access to denosumab treatment of osteoporosis.
- 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 funding for denosumab be widened with a medium priority such that:
- patients contraindicated to all bisphosphonate therapy would no longer have to try a funded antiresorptive agent for 12 months; and
  - patients intolerant to all bisphosphonate therapy, making them unusable, would no longer have to try a funded antiresorptive agent for 12 months.
- 4.4. The Committee **recommended** widening the denosumab criteria by amending criteria 4 as follows (additions in bold):
- 4 **Either:**
- 4.1** Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 mL/min; **or**
  - 4.2 The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with zoledronic acid;** and
- but only if the proposal would be cost-neutral to the cost of zoledronic acid treatment, including any administration costs paid for by patients.
- 4.5. The Committee **recommended** that the proposal to widen access to denosumab by removing the specific definition of "contraindicated to zoledronic acid" be declined.

## Discussion

- 4.6. The Committee noted that denosumab had been funded as of 1 July 2018, subject to restrictions recommended by PTAC and its Endocrinology Subcommittee. The committee noted that feedback on the consultation to list denosumab had proposed a number of ways to widen access, and that the supplier of denosumab had also submitted a new application proposing widening access.
- 4.7. The Committee considered that it had previously described the need of patients with osteoporosis in this general group. Members noted that even with use of bisphosphonates patients with osteoporosis still have a relatively high risk of fractures and that adverse effects of bisphosphonates can contribute to treatment discontinuation. The committee considered that patients who would gain funding if the supplier's changes were made had a similar health need to the already funded groups. Members noted that some patients did not have as many alternative treatments, in particular patients who cannot tolerate bisphosphonates or those with severe renal impairment.
- 4.8. The Committee considered that it had previously reviewed the key clinical trials for denosumab, in particular the pivotal FREEDOM trial (Cummings et al N Engl J Med 2009;361:756-65) in postmenopausal women. Members noted that there are no head-to-head trials of denosumab against other agents that reported fracture outcomes. Members considered that there is good evidence of a benefit over placebo, and weak evidence of superiority to bisphosphonates based on surrogate outcomes. Members considered that, unlike bisphosphonates, when stopping denosumab, the benefits are rapidly and fully lost, though members considered that it had seen no evidence to suggest that this loss of benefit leads to a worse state than before treatment.
- 4.9. The Committee discussed the ADAMO trial (Orwoll et al J Clin Endocrinol Metab 2012;97:3161-9), which had been reviewed by the Endocrinology Subcommittee but not by PTAC. The committee noted that the trial used a surrogate endpoint of change in bone mineral density, and that the trial showed increases in bone mineral density at all sites assessed compared with placebo.

- 4.10. The Committee discussed the evidence for the use of denosumab second-line after another treatment. The Committee reviewed the meta-analysis by Fontalis et al (Expert Opinion on Drug Safety 2018;17:413-28), and noted that PTAC had reviewed three of the five studies used in its primary outcome while the other two included ibandronate or teriparatide which are not used in this setting in New Zealand. Members considered the studies where oral bisphosphonates were used as the comparator, and considered that in this subset of studies the reported improvement in BMD versus comparator was lower than in the study as a whole (1.18%, 95% CI 0.76-1.60, instead of 1.59%, 95% CI 1.01-2.17). The committee considered that based on this evidence, denosumab is likely to be no worse than bisphosphonates but evidence that it is better in second line is relatively weak and limited to surrogate endpoints.
- 4.11. The Committee discussed the four separate ways that the supplier had proposed to widen access, and also discussed other possible ways to widen access.

#### Contraindicated to all bisphosphonates

- 4.12. The Committee reviewed the proposal to allow patients who are contraindicated to all funded bisphosphonates to be exempt from the requirement to trial an alternate agent for 12 months.
- 4.13. Members noted that it had recommended the requirement to trial another agent because other agents such as alendronate and risedronate had comparable efficacy to denosumab but were a lower price.
- 4.14. The Committee reviewed contraindications and cautions from the Medsafe datasheets for bisphosphonates. The committee considered that the majority of issues were a class effect, meaning that if a patient was contraindicated to zoledronic acid, they would likely also be contraindicated to all bisphosphonates.
- 4.15. The Committee considered that if patients were contraindicated to all funded bisphosphonates, then there was most likely no alternative funded effective option available to them. Members considered that raloxifene was unsuitable in most patients due to having limited efficacy and significant adverse events especially in women over 50, and that it was not indicated in men with osteoporosis.
- 4.16. The Committee considered that the requirement to try another agent before accessing denosumab was inappropriate in this patient group.

#### Intolerant to all bisphosphonates

- 4.17. The Committee reviewed the proposal to allow patients who are unable to take any funded bisphosphonate, due to intolerance, to be exempt from the requirement to trial an alternate agent for 12 months. Members noted that PTAC had recommended that requirement because other agents, such as alendronate and risedronate, were similarly effective as denosumab but were a lower price.
- 4.18. The Committee noted that oral bisphosphonates can cause upper gastrointestinal adverse events, such as oesophageal stricture, or poorly controlled oesophageal reflux, as well as musculoskeletal pain. Members also noted that zoledronic acid infusions can cause acute phase reactions or uveitis.
- 4.19. The Committee considered that where adverse reactions prevent the use of bisphosphonates, there are no effective funded options. Members considered that raloxifene was unsuitable in most patients due to having limited efficacy and significant adverse events especially in women over 50, and that it was not indicated in men with osteoporosis.

- 4.20. The Committee considered that the term ‘intolerance’ is difficult to define within a Special Authority and carries a risk of slippage to patients who have adverse events with bisphosphonates but are able to continue using them. Members noted that many adverse events are manageable, but if intolerance leads to non-adherence, then there may be health benefits lost. Members noted that adherence to bisphosphonates is typically poor, and considered that the evidence shows denosumab has improved adherence.
- 4.21. The Committee considered that the requirement to try another agent before accessing denosumab was inappropriate for patients who are unable to take bisphosphonates due to intolerance.

#### Fractured while on zoledronic acid

- 4.22. The Committee noted that the current criteria require a patient to be contraindicated to zoledronic acid. The committee noted the applicant’s proposal that a patient could also meet this criterion if they have tried zoledronic acid for at least 12 months and have had a fracture during this time. Members noted that this would only be one dose of zoledronic acid as it is dosed once every 12 months.
- 4.23. The Committee noted it had previously concluded that denosumab and zoledronic acid provided similar benefits in reducing the risk of a fracture.
- 4.24. The Committee noted that with zoledronic acid there was a direct patient cost for administration, and considered this cost was a barrier to accessing treatment.
- 4.25. Members considered there was a safety issue with starting on denosumab after a zoledronic acid dose, since the zoledronic acid would stay in the body causing a ‘double dose’ and increasing the risk of osteonecrosis of the jaw.
- 4.26. The Committee considered that a fracture on zoledronic acid does not alter the effects of zoledronic acid in lowering the risk of another fracture, which meant that switching to the equally effective denosumab would not provide any health benefits. The committee considered that if denosumab treatment cost less than zoledronic acid treatment, including the patient’s administration fee, then this change would be appropriate.

#### Wider definition of ‘contraindicated to zoledronic acid’

- 4.27. The Committee discussed the supplier’s proposal to amend current criteria 4 to remove the text “because the patient’s creatinine clearance is less than 35 mL/min”. The members noted this would leave the judgement of “contraindication to zoledronic acid” to the clinician and would allow other reasons for contraindication.
- 4.28. The Committee noted it had previously recommended including a definition of this term to ensure treatments are used appropriately.
- 4.29. The Committee considered that this amendment carried too large a risk of widespread use of denosumab outside of the intended group, due to leaving “contraindicated” too ill-defined.

#### Other patient groups

- 4.30. The Committee discussed whether premenopausal women, or any subgroups of those patients, might be appropriate for denosumab funding. Members noted that denosumab is not indicated by Medsafe for this group.
- 4.31. Members noted that there is a Phase I study underway looking at denosumab in women with anorexia nervosa. Members discussed if the supplier could present an application on this group.

## 5. Obinutuzumab for the treatment of Non-Hodgkin's Lymphoma who relapse or are refractory to, a rituximab regimen and the treatment of Follicular Lymphoma

### Application

#### 5.1. The Committee reviewed:

- 5.1.1. An application for obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of indolent non-Hodgkin's lymphoma (NHL) which has relapsed after, or is refractory to, a rituximab-containing regimen.
- 5.1.2. An application for obinutuzumab for use in combination with chemotherapy for the first-line induction and maintenance treatment of follicular lymphoma.

#### 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 obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of indolent non-Hodgkin's lymphoma which has relapsed after, or is refractory to, a rituximab-containing regimen be listed with a low priority.

- 5.3.1. The Committee **recommended** that the application for obinutuzumab for relapsed/refractory indolent non-Hodgkin's lymphoma (NHL) be referred to the Cancer Treatment Subcommittee of PTAC (CaTSoP) for advice regarding the need for obinutuzumab in NHL and the potential impact of increasing infusion requirements due to maintenance therapy.

#### 5.4. The Committee **recommended** that obinutuzumab for use in combination with chemotherapy for the first-line induction and maintenance treatment of follicular lymphoma be deferred until additional data is made available regarding the long-term safety of obinutuzumab and the likely efficacy of obinutuzumab retreatment or rituximab containing regimens at relapse following first-line obinutuzumab.

- 5.4.1. The Committee **recommended** that the application for obinutuzumab for the first-line induction and maintenance treatment of follicular lymphoma be referred to CaTSoP for advice regarding the potential health benefits of obinutuzumab in this setting.

### General Discussion

#### 5.5. The Committee noted that 85% to 90% of NHLs are B-cell derived, and that the majority express CD20. The Committee noted that there are a number of different types of NHL, and that they can be clinically divided into indolent (e.g. follicular lymphoma), aggressive (e.g. diffuse large B-cell lymphoma), and hyper aggressive malignancies (e.g. Burkitt lymphoma).

#### 5.6. The Committee noted that the incidence of NHL in New Zealand in 2015 was 12 per 100,000 population (including indolent and aggressive types) and is increasing slightly over time. The Committee noted that 63% of patients diagnosed with NHL are 65 years or older, that the incidence is slightly higher in men than women, and that the incidence is similar in Māori and non-Māori.

#### 5.7. The Committee noted that obinutuzumab is a glycoengineered type II anti-CD20 antibody that targets the extracellular loop of the CD20 transmembrane antigen on the surface of B-cells and pre-B-cells. The Committee noted that type II anti-CD20 antibodies work primarily

by inducing direct cell death, whereas type I anti-CD20 antibodies (such as rituximab) work primarily via antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated phagocytosis, and complement-dependent cytotoxicity. The Committee considered that it is unclear how clinically significant the difference is between type I and type II anti-CD20 antibodies, but considered it was plausible there was a significant functional difference given the evidence of clinical responses in rituximab refractory patients.

- 5.8. The Committee noted that the recommended dosing regimen of obinutuzumab for follicular lymphoma or relapsed/refractory NHL is 1000 mg administered on Days 1, 8, and 15 of Cycle 1; and 1000 mg on Day 1 of Cycles 2 to 8 (21 days cycles) or Cycles 2 to 6 (28-day cycles). Maintenance therapy involves obinutuzumab 1000 mg once every two months for up to two years or until progression.
- 5.9. The Committee noted that obinutuzumab is funded in New Zealand for the treatment of chronic lymphocytic leukaemia subject to Special Authority criteria.

#### Obinutuzumab for relapsed/refractory indolent NHL

- 5.10. The Committee noted that approximately 14% of patients with NHL will experience rituximab-refractory disease or will experience relapse within six months of rituximab treatment. The Committee noted that in New Zealand, relapsed/refractory patients with indolent NHL are most commonly treated with bendamustine (funded since July 2017).
- 5.11. The Committee noted the open-label, phase 3, GADOLIN trial, which investigated the efficacy and safety of induction therapy with obinutuzumab plus bendamustine followed by obinutuzumab maintenance compared with induction therapy with bendamustine monotherapy in patients with rituximab-refractory indolent NHL ([Sehn et al. Lancet Oncol. 2016;17:1081-1093](#)). The Committee noted that the GADOLIN trial provides the primary evidence for the efficacy of obinutuzumab in combination with bendamustine for the treatment of rituximab relapsed/refractory NHL.
- 5.12. The Committee noted the study design and eligibility criteria of the GADOLIN trial. In general, the Committee considered that the patient population was relevant to the New Zealand population; however, it was noted that the requirement for patients to have an estimated life expectancy of five years may have selected for a healthy relapsed/refractory indolent NHL population.
- 5.13. The Committee noted that the GADOLIN trial recruitment ceased at the time of the protocol-specified interim efficacy analysis, as the primary endpoint had been met (stopping criteria, one-sided *P*-value no greater than 0.0075 and a HR of 0.68). The Committee noted that a total of 396 patients were enrolled between April 2010 and September 2014, and that, at the time of stopping, progression-free survival (PFS) events had occurred in 71 (37%) patients in the obinutuzumab plus bendamustine group and 104 (51%) patients in the bendamustine monotherapy group.
- 5.14. The Committee noted the baseline demographic and clinical characteristics of the GADOLIN trial population. The Committee considered that the proportion of patients with a Follicular Lymphoma-specific International Prognostic Index (FLIPI) score of low, and the proportion of patients who had received only one prior treatment regimen, was higher in the obinutuzumab plus bendamustine group compared with the bendamustine monotherapy group, possibly leading to some overestimation of the benefit of obinutuzumab.
- 5.15. The Committee noted that the median follow-up in the GADOLIN trial was 21.9 months in the obinutuzumab plus bendamustine group compared with 20.3 months in the bendamustine monotherapy group. The Committee noted that the median PFS was not reached in the obinutuzumab plus bendamustine group compared with 14.9 months in the

- bendamustine monotherapy group (HR 0.55; 95% CI, 0.40-0.74;  $P=0.0001$ ). The Committee noted that median overall survival (OS) had not been reached in either treatment arm.
- 5.16. The Committee noted that the subgroup analysis conducted in the GADOLIN trial reported no statistically significant differences in PFS between subgroups.
  - 5.17. The Committee noted that there was no substantial difference in toxicity between the treatment groups in the GADOLIN trial during the induction phase; however, the Committee also noted that a number of adverse events were reported in the obinutuzumab maintenance phase, and it was considered that these may endure for a significant period of time.
  - 5.18. The Committee noted the updated analysis of the phase 3 GADOLIN trial which had a clinical cut-off date of April 2016, providing a median of 11 months of additional follow-up (Cheson et al. *J Clin Oncol.* 2018;36:2259-66). The Committee noted that the median follow-up in the updated analysis was 34 months in the obinutuzumab plus bendamustine group and 30 months in the bendamustine monotherapy group.
  - 5.19. The Committee noted that the median PFS in the updated GADOLIN analysis was 25.8 months in the obinutuzumab plus bendamustine group compared with 14.1 months in the bendamustine monotherapy group (HR 0.57; 95% CI 0.44-0.73;  $P<0.001$ ); median OS was not reached for either treatment arm, although the reported HR for OS was: 0.67; 95% CI 0.47-0.96;  $P=0.0269$ .
  - 5.20. The Committee noted the GADOLIN trial was not powered to detect a difference in OS between the treatment groups, and only a small number of OS events had occurred (57 OS events in the obinutuzumab plus bendamustine group and 73 OS events in the bendamustine monotherapy group).
  - 5.21. The Committee noted a secondary analysis of health-related quality of life (HRQoL) data from the GADOLIN trial ([Cheson et al. \*Ann Hematol.\* 2017;96:253-9](#)). The Committee considered that there was no substantial difference in HRQoL between the obinutuzumab plus bendamustine group and the bendamustine monotherapy group.
  - 5.22. The Committee considered that the results of the GADOLIN trial demonstrated that induction therapy with obinutuzumab plus bendamustine followed by maintenance therapy with obinutuzumab improved PFS compared with induction therapy with bendamustine alone, but that there was uncertain evidence of an OS benefit. The Committee further considered that there was no significant difference in safety or HRQoL between the treatment groups.
  - 5.23. The Committee considered that patients with rituximab relapsed/refractory NHL already have access to bendamustine, and that it remains unclear if there is a need in the treatment paradigm for an additional agent. The Committee further considered that the addition of an obinutuzumab maintenance therapy phase may have a significant impact on DHB infusion services. The Committee considered that additional input on these matters is required from CaTSoP.

#### Obinutuzumab for first-line follicular lymphoma

- 5.24. The Committee noted that staging of follicular lymphoma is carried out according to the Ann Arbor classification system, which is based on area of lymph node involvement. The Committee noted that for prognostic purposes the FLIPI is used, which categorizes patients as low, intermediate, or high risk based on patient characteristics including number of nodal sites, age, serum markers, follicular lymphoma stage, and haemoglobin levels.

- 5.25. The Committee noted the European Society for Medical Oncology treatment guidelines for follicular lymphoma ([Dreyling et al. Ann Oncol. 2016;27:v83-v90](#)). The Committee noted that for asymptomatic patients, a watch and wait approach is recommended; for patients exhibiting mild symptoms, single agent rituximab or radioimmunotherapy is recommended; and for patients with a high tumour burden, rituximab in combination with chemotherapy followed by rituximab maintenance is recommended.
- 5.26. The Committee noted that in New Zealand, symptomatic patients with follicular lymphoma are treated with induction therapy of six cycles of rituximab (funded since July 2009) with or without chemotherapy. The Committee noted that rituximab maintenance therapy for follicular lymphoma is not currently funded in New Zealand, but that an application for rituximab maintenance therapy for CD20+ low-grade or follicular B-cell NHL received a medium priority recommendation from [CaTSoP in April 2018](#).
- 5.27. The Committee noted the open-label, phase 3, GALLIUM trial, which investigated the efficacy and safety of induction therapy with obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy followed by maintenance therapy with the same monoclonal antibody in patients with previously untreated indolent NHL ([Marcus et al. N Engl J Med. 2017;377:1331-44](#)). The Committee noted that the GALLIUM trial provides the primary evidence for the efficacy of obinutuzumab induction and maintenance therapy for the first-line treatment of follicular lymphoma.
- 5.28. The Committee noted the study design and eligibility criteria of the GALLIUM trial. The Committee noted that patients included in the GALLIUM trial were required to meet the Groupe d'Étude des Lymphomes Folliculaires (GELF) high tumour burden criteria, which included having bulky disease, systemic symptoms, elevated serum markers, or B symptoms. The Committee also noted that approximately 60% of patients received bendamustine as their chemotherapy regimen.
- 5.29. The Committee noted that the results of GALLIUM reported in Marcus et al. 2017 were from a prespecified interim analysis that was scheduled to take place after approximately 67% of the 370 events of progression, relapse, or death, required for the primary analysis had occurred. The Committee noted that the pre-specified analysis was carried out after 245 events had occurred (101 in the obinutuzumab group, and 144 in the rituximab group).
- 5.30. The Committee noted that after a median follow-up of 34.5 months, the 3-year PFS rate in the GALLIUM trial was 80.0% in the obinutuzumab group compared with 73.3% in the rituximab group (HR 0.66; 95% CI 0.51-0.85;  $P=0.001$ ). The Committee noted that the 3-year OS rate was 94.0% in the obinutuzumab group compared with 92.1% in the rituximab group (HR 0.75; 95% CI 0.49-1.17;  $P=0.21$ ).
- 5.31. The Committee noted that the estimated 3-year rate of no new anti-lymphoma treatment in the GALLIUM trial was 87.1% in the obinutuzumab group compared with 81.2% in the rituximab group (HR 0.68, 95% CI 0.51-0.91;  $P=0.009$ ). The Committee noted that the overall response rate and complete response rate at the end of induction therapy were similar between the treatment groups.
- 5.32. The Committee noted that there was no significant difference in toxicity between the treatment groups in the GALLIUM trial but noted that a slight increase in the rate of infusion-related reactions in the obinutuzumab group may have an impact on healthcare resources.
- 5.33. The Committee noted a letter to the editor regarding the GALLIUM trial ([Nair et al. N Engl J Med. 2017;377:2605](#)). The Committee noted a number of issues raised in this correspondence, including: that more than half of patients in GALLIUM received bendamustine-based induction therapy and that there is no evidence yet demonstrating a benefit of maintenance therapy after bendamustine induction; that there is no mention of response to retreatment, which is standard following first-line rituximab; and that there is a

question as to whether the PFS advantage of 7% is worth the 7% increase in grade 3-5 adverse events.

- 5.34. The Committee considered that the results of the GALLIUM trial demonstrated that induction and maintenance therapy with obinutuzumab improved PFS compared with induction and maintenance therapy with rituximab. The Committee further considered that there was no evidence of a quality of life benefit and no clear evidence of an OS benefit with obinutuzumab compared with rituximab.
- 5.35. The Committee considered that the primary concern for oncologists regarding the potential listing of first-line obinutuzumab would be the lack of evidence regarding treatment sequencing and whether obinutuzumab would be preferred over rituximab maintenance in the setting. The Committee considered that the current standard of care involves serial lines of rituximab-containing therapy, and that there is a lack of data regarding whether re-treatment with an anti-CD20 antibody will be safe and effective following first-line treatment with obinutuzumab. The Committee considered that based on the evidence available at this time, the preferred option would be to fund rituximab maintenance initially, with obinutuzumab maintenance funded only if cost-neutral to rituximab maintenance.

## **6. Alectinib for the first-line treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer**

### Application

- 6.1. The Committee reviewed the application for alectinib for the first-line treatment of anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic, non-small cell lung cancer (NSCLC); and letter of support from a clinician for the funding of alectinib as a first-line treatment for ALK-positive advanced NSCLC.
- 6.2. The Committee further considered the application for crizotinib for the first-line treatment of ALK-positive NSCLC in light of the final published overall survival results.
- 6.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Recommendation

- 6.4. The Committee **recommended** that alectinib be funded for the first-line treatment of ALK-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) with medium priority.
- 6.5. The Committee also **recommended** that the application be referred to the Cancer Treatments Subcommittee of PTAC for advice regarding appropriate Special Authority criteria.
- 6.6. The Committee reiterated its previous **recommendation** that crizotinib for the first- and second-line treatment of ALK-positive advanced NSCLC be declined due to concerns regarding trial design and poor cost-effectiveness at the proposed price.

### Discussion

- 6.7. The Committee noted that NSCLC is the most common type of lung cancer, accounting for approximately 75% of all cases. The Committee noted that approximately 4-5% of NSCLC patients have ALK-positive disease; the vast majority of which are reported in non-squamous NSCLC and are generally mutually exclusive with EGFR or KRAS mutations.
- 6.8. The Committee noted that patients with ALK-positive NSCLC have a poorer prognosis than NSCLC associated with other oncogenic drivers and generally have a more advanced

stage of disease at diagnosis. The Committee noted that patients with ALK-positive NSCLC also have a high lifetime risk of central nervous system (CNS) metastases and a relatively high frequency (25%) of brain metastases at diagnosis, which are associated with a significant reduction in prognosis and health-related quality of life.

- 6.9. The Committee noted that advanced lung cancer is considered incurable and that platinum chemotherapy and pemetrexed is the current standard of care in New Zealand for all lung cancer patients with or without ALK mutation. The Committee also noted that oral tyrosine kinase inhibitors, gefitinib or erlotinib, were funded for patients with NSCLC expressing activating mutations in EGFR tyrosine kinase.
- 6.10. The Committee noted that alectinib is a second-generation ALK-targeted tyrosine kinase inhibitor for which the evidence provided was for the treatment of adult patients with ALK-positive, locally advanced or metastatic NSCLC compared to crizotinib.
- 6.11. The Committee noted that the currently a registered indication for alectinib in NZ as stated on the Medsafe datasheet is 'for the treatment of adult patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib'. The Committee noted that the supplier has indicated it had applied for an amendment to the Medsafe registration to include the requested indication.

#### Crizotinib

- 6.12. The Committee noted that in November 2015 and August 2016 PTAC had recommended that funding for crizotinib (a first-generation ALK inhibitor) for the first- and second-line treatment of ALK-positive advanced NSCLC be declined due to concerns regarding trial design, lack of long-term efficacy data and poor cost-effectiveness at the proposed price.
- 6.13. The Committee noted that CaTSoP had recommended funding in May 2016 for crizotinib for both first and second-line with low priority and had noted that CaTSoP's recommendation was influenced by the high health need of the population.
- 6.14. The Committee noted that since its previous consideration of crizotinib the final overall survival (OS) results had been published from PROFILE1014 – a phase 3, open label, randomised trial of crizotinib versus first-line pemetrexed and platinum chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in treatment naïve patients with advanced ALK-positive non-squamous NSCLC ([Soloman et al. J Clin Oncol. 2018; doi: 10.1200/JCO.2017.77.4794. \[Epub ahead of print\]](#)).
- 6.15. The Committee noted that after a median follow up duration of approximately 46 months for both arms, that median OS was not reached with crizotinib compared with 47.5 months for chemotherapy (HR 0.760; 95% CI 0.548-1.053;  $P = 0.0978$ ). Members noted that the HR for OS did not reach statistical significance.
- 6.16. The Committee noted that 92 patients (53.5%) in the crizotinib arm and 148 patients (86.5%) in the chemotherapy arm received at least one systemic anticancer treatment after study treatment. The Committee considered that could have influenced the lack of a statistically significant difference in OS; however, the level of benefit from crizotinib remained uncertain. The Committee considered that issues with trial design and poor cost-effectiveness at the proposed price previously noted by PTAC remained relevant.

#### Alectinib

- 6.17. The Committee noted the key evidence for the use of alectinib for the treatment of ALK-positive advanced NSCLC comes from the ALEX study ([Peters et al. N Engl J Med. 2017;377:829-38](#): a phase 3, randomised, open-label study of 303 previously untreated ALK-positive advanced NSCLC patients who received alectinib (600 mg bd) or crizotinib (250 mg bd).

- 6.18. The Committee noted that per protocol, crossover between trial groups was not allowed, but that patients in the crizotinib arm may have received alectinib after disease progression in countries where this was available.
- 6.19. The Committee noted eligibility criteria included measurable disease according to RECIST v1.1 and adequate hepatic, renal and bone marrow function. The Committee noted that patients with asymptomatic CNS disease were eligible, and previous CNS radiotherapy completed at least 14 days prior to enrolment was allowed.
- 6.20. The Committee noted that after a median follow-up of 17.6 months (crizotinib) and 18.6 months (alectinib), the median investigator-assessed PFS, the primary endpoint, was not reached for alectinib (95% CI, 17.7 months to not estimable), as compared with 11.1 months (95% CI, 9.1 to 13.1) with crizotinib (HR for disease progression or death, 0.47 [95% CI, 0.34 to 0.65];  $P < 0.001$ ).
- 6.21. The Committee noted that independent review committee–assessed time to CNS progression was longer in the alectinib arm compared with the crizotinib arm (cause-specific HR 0.16, 95% CI 0.10-0.28;  $P < 0.001$ ). Members noted that 12% of patients in the alectinib arm compared with 45% in the crizotinib arm had an event of CNS progression.
- 6.22. The Committee noted that for patients with measurable CNS lesions at baseline, a CNS response occurred in 81% (95% CI, 58 to 95) in the alectinib group and 50% (95% CI, 28 to 72) in the crizotinib group. The Committee noted that 8 patients (38%) in the alectinib group had a complete CNS response as compared with 1 patient (5%) in the crizotinib group; and the median duration of intracranial response was 17.3 months (95% CI, 14.8 to not estimable) and 5.5 months (95% CI, 2.1 to 17.3), respectively.
- 6.23. The Committee considered that ALEX was a high-quality study, although noted limitations including its open-label design, investigator assessed endpoint, that it was not powered to detect OS difference, and that any survival data was likely to be confounded by patients receiving post-progression treatments off-trial.
- 6.24. The Committee noted evidence for the use of alectinib from the J-ALEX study (Hida et al. *Lancet*. 2017;390:29-39; Takiguchi et al. *J Clin Oncol*. 2017;35(no. )15\_suppl):9064): a randomised, open-label, phase 3 Japanese study of alectinib versus crizotinib in previously untreated or one line of chemotherapy advanced ALK-positive NSCLC.
- 6.25. The Committee considered additional evidence for the use of alectinib in the treatment of ALK-positive advanced NSCLC including from:
- Camidge et al. 2018 ASCO Annual Meeting. Abstract no. 9043
  - Seto et al. *Lancet Oncol*. 2013;14:590-8; Tamura et al. *J Clin Oncol*. 2017;35:1515-21
- 6.26. The Committee noted that there appeared to be no head-to-head comparison data of alectinib versus the standard of care in New Zealand, platinum-pemetrexed chemotherapy.
- 6.27. The Committee noted the supplier’s indirect comparison using the Bucher method using crizotinib and ceritinib; and considered that there were inherent difficulties with any indirect comparison including controlling for baseline heterogeneity.
- 6.28. The Committee noted there is no trial data available regarding the use of alectinib as second-line treatment following chemotherapy only, but noted trial data for alectinib as a second- and third-line treatment following crizotinib ([Shaw et al. \*Lancet Oncol\*. 2016;17:234-42](#); [Novello et al. \*Ann Oncol\*. 2018;29:1409-16](#)). However, the Committee considered this was relevant to consideration of a second-line treatment for a New Zealand population as crizotinib was not currently funded for the treatment of ALK-positive advanced NSCLC.

- 6.29. The Committee considered that currently available evidence suggests there is a class effect from ALK-targeted TKIs as first-line treatments of advanced NSCLC disease outside the CNS, and that these agents could be considered therapeutically equivalent for ALK-positive advanced NSCLC without CNS.
- 6.30. The Committee noted that other ALK targeted treatments for ALK-positive advanced NSCLC are in development and would likely be brought to market.
- 6.31. The Committee considered that due to the differential mechanism of action alectinib had improved CNS penetration as compared with crizotinib.
- 6.32. The Committee considered that based on currently available evidence alectinib appears to have a more favourable effect on CNS outcomes and an improved safety profile compared with crizotinib.
- 6.33. The Committee considered that there appeared to be a clinically relevant effect from treatment with these agents, and that current evidence provided a higher degree of certainty regarding the level of benefit from alectinib compared to crizotinib.
- 6.34. The Committee considered that, as with crizotinib, it was likely that further data would show the development of a resistance mechanism to alectinib; and as such, all patients would progress past treatment with an ALK-targeted agent. The Committee considered that the majority would go on to receive a further line of treatment as this population would generally be fitter than the average lung cancer patient.

## 7. Cetuximab for the first line treatment of RAS-wild-type, left-sided metastatic colorectal cancer

### Application

- 7.1. The Committee reviewed the application for cetuximab for the first-line treatment of *RAS* wild-type, left-sided metastatic colorectal cancer (mCRC)
- 7.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Recommendation

- 7.3. The Committee **recommended** that the application for cetuximab for the treatment of *RAS* wild-type, left-sided metastatic colorectal cancer be declined.
- 7.4. The Committee **recommended** that the application for cetuximab for the treatment of *RAS* wild-type, left-sided metastatic colorectal cancer (mCRC) be referred to the Cancer Treatment Subcommittee of PTAC (CaTSoP) for advice regarding EGFR-inhibition in mCRC generally as well as anatomically defined sub-populations of mCRC.

### Discussion

- 7.5. The Committee noted that CRC is an area of high health need in New Zealand. In addition to having one of the highest incidence rates for CRC in the world (41.1 per 100,000 population from Ministry of Health Cancer Registry data), New Zealand also has high mortality rates, and a high rate of metastatic disease at diagnosis (24% for colon; 19% for rectal based on [PIPER project data](#)).
- 7.6. The Committee noted that left-sided colorectal cancers (CRCs) are derived from the embryologic hindgut and originate in the distal third of the transverse colon, the splenic flexure, the descending colon, the sigmoid colon, and the rectum.

- 7.7. The Committee noted that left-sided CRCs are commonly associated with chromosomal abnormalities; *KRAS*, *DCC*, and *p53* mutations; *HER1* and *HER2* gene amplification; aneuploidy; and gene expression profiles consistent with sensitivity to EGFR-targeted therapies. The Committee also noted that left-sided CRCs are more commonly associated with familial adenomatous polyposis; in contrast, hereditary non-polyposis CRC most commonly occurs in the right-sided colon.
- 7.8. The Committee noted that left-sided CRCs occur more commonly in men and are generally associated with a better prognosis than right-sided colonic cancers.
- 7.9. The Committee noted that standard of care for the treatment of first-line mCRC in New Zealand is generally chemotherapy with FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin), although FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) is also used.
- 7.10. The Committee noted that cetuximab for the treatment of mCRC has been reviewed previously and declined by PTAC and CaTSoP for:
- patients with *KRAS* wild-type mCRC refractory to irinotecan and oxaliplatin ([CaTSoP minutes – September 2013](#), [PTAC minutes – February 2014](#)), and
  - the first-line neoadjuvant treatment of patients with *KRAS* wild-type mCRC whose metastases are limited to the liver in combination with irinotecan-based chemotherapy ([PTAC minutes – August 2014](#), [CaTSoP minutes – October 2014](#)).
- 7.11. The Committee noted that cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) on tumour and normal cells, thereby preventing ligand binding and subsequent activation of the EGFR signalling pathway.
- 7.12. The Committee noted a retrospective analysis of the phase 3 CRYSTAL and FIRE-3 trials that investigated the potential prognostic and predictive value of primary tumour location in patients with *RAS* wild-type mCRC treated with first-line FOLFIRI plus cetuximab ([Tejpar et al. JAMA Oncol. 2017;3:194-201](#)).
- 7.13. The Committee noted that they had previously considered the result of the CRYSTAL study ([Van Cutsem et al. N Engl J Med. 2009;360:1408-17](#)) during the prior consideration of cetuximab for mCRC. The Committee noted that the results of FIRE-3 had not been previously considered by PTAC; however, it was considered that, as this study investigated FOLFIRI/cetuximab against FOLFIRI/bevacizumab in the first-line treatment of mCRC, this evidence was of limited relevance to the New Zealand setting as bevacizumab is not funded for the treatment of CRC in New Zealand.
- 7.14. The Committee considered that the post-hoc, retrospective Tejpar et al. analysis of CRYSTAL reported that patients with left-sided tumours who received FOLFIRI plus cetuximab appeared to have improved outcomes relative to FOLFIRI alone, and that an interaction was observed between primary tumour location and treatment for overall survival (OS) (CRYSTAL: HR 1.95, 95% CI 1.09-3.48; FIRE-3: HR 0.40, 95% CI 0.23-0.70); however, the Committee noted the wide confidence intervals and considered there were issues with interpretation of a retrospective, post-hoc analysis of studies with relatively small subgroup sizes and imbalances in baseline characteristics between treatment arms.
- 7.15. The Committee noted a retrospective analysis of aggregated data from six clinical trials that investigated the prognostic and predictive value of primary tumour side in patients with *RAS* wild-type mCRC treated with chemotherapy and EGFR-directed antibodies ([Arnold et al. Ann Oncol. 2017;28:1713-29](#)). The Committee noted that three of these were cetuximab studies (CRYSTAL, FIRE-3 and CALGB80405). The Committee considered that the CALGB80405 study which included bevacizumab in the comparator arm was of less relevance to a New Zealand setting.

- 7.16. The Committee noted that the retrospective Arnold et al. analysis indicated that median OS, progression free survival (PFS), and overall response rate (ORR) were better for patients with left-sided tumours across all studies, with a greater treatment effect seen in patients who received chemotherapy plus cetuximab compared with patients who received chemotherapy plus bevacizumab. The Committee also noted that the subset analysis demonstrated an OS benefit with chemotherapy plus cetuximab compared with chemotherapy alone in patients with left-sided tumours (HR 0.69; 95% CI 0.59-0.80;  $P < 0.001$ ). The Committee considered that as this was a retrospective analysis the results should be interpreted with caution.
- 7.17. The Committee noted a meta-analysis of five retrospective and exploratory studies that evaluated the efficacy of adding anti-EGFR monoclonal antibodies (mAB; i.e. cetuximab, panitumumab) to oxaliplatin-based regimens for the treatment of *RAS* wild-type left-sided mCRC ([Chen et al. \*Medicine \(Baltimore\)\*. 2018;97:e0097](#)). The Committee noted that the meta-analysis indicated the addition of an anti-EGFR mAB to FOLFOX appeared to improve efficacy in patients with left-sided mCRC (OS: HR 0.77, 95% CI 0.61-0.98,  $P = 0.03$ ; PFS: HR 0.68, 95% CI 0.57-0.82,  $P < .00001$ ); however, the Committee considered that this was a systematic review of retrospective and exploratory studies, which could be susceptible to bias favouring the treatment in left-sided mCRC, with consequent issues regarding interpretation of the results.
- 7.18. The Committee noted a consensus statement from Canadian mCRC experts regarding the predictive effect of primary tumour location in the treatment of mCRC ([Abrahamo et al. \*Curr Oncol\*. 2017;24:390-400](#)).
- 7.19. The Committee considered that the currently available evidence for the efficacy of cetuximab in left-sided *RAS* wild-type mCRC was based solely on retrospective analyses and was therefore of weak strength and low quality. The Committee considered the relative benefit of cetuximab was uncertain and associated with a level of toxicity.
- 7.20. The Committee noted that cetuximab has been approved for use internationally for mCRC irrespective of anatomical location and considered it unlikely that any prospective clinical trials designed specifically to investigate the efficacy of cetuximab in left-sided mCRC would be conducted.
- 7.21. Members considered that there have been advances in the understanding of CRC since cetuximab was approved for use internationally which suggest there may be a difference in left- versus right-sided mCRC. Members considered that there is an expanding evidence base indicating differential needs for CRC sub-populations and considered that advice should be sought from the Cancer Treatments Subcommittee to inform any further consideration of the use of cetuximab in anatomically or molecularly defined mCRC sub-populations.
- 7.22. The Committee noted that the applicant had indicated the potential to administer cetuximab fortnightly at a dose of 500 mg/m<sup>2</sup> in combination with FOLFIRI, rather than the datasheet specified 250 mg/m<sup>2</sup> weekly dosing. The Committee considered that the evidence to support fortnightly dosing of cetuximab at 500 mg/m<sup>2</sup> appeared to be in a second-line setting and there was a lack of evidence to support its use in the first-line setting.

## **8. Tenofovir alafenamide in the treatment of chronic hepatitis B**

### Application

- 8.1. The Committee reviewed the application for tenofovir alafenamide in the treatment of chronic hepatitis B.
- 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 tenofovir alafenamide be listed as cost neutral to the tenofovir disoproxil salts.

## Discussion

- 8.4. The Committee noted that tenofovir alafenamide (TAF) is a novel nucleotide reverse transcriptase inhibitor (NRTI) that has demonstrated high antiviral efficacy at a dose less than one-tenth that of tenofovir disoproxil (TDF). The Committee considered that the application was based on a superiority in side effects profile compared to TDF due to higher concentration of active metabolite in cells and a corresponding lower plasma exposure resulting in a decrease in renal and bone toxicity.
- 8.5. The Committee considered that alternative treatments to TAF for chronic hepatitis B (CHB) have reduced dosing recommendations in renal impairment. The Committee did not consider that the application adequately addressed if there was an unmet need in the CHB patient group in patients that have experienced renal and bone toxicity from the use of TDF who could not use other funded alternatives.
- 8.6. The Committee noted that the New Zealand datasheet for TDF stated that clinical relevant bone abnormalities have not been seen in long-term clinical studies in adults.
- 8.7. The Committee considered that the application did not provide a clear indication of desired patient group with precise special authority criteria. Members noted that chronic kidney disease was described as eGFR less than 60 ml/min/1.72m<sup>2</sup> and osteoporosis was not formally defined.
- 8.8. The Committee noted that there are no head-to-head comparison of tenofovir alafenamide and entecavir. Members considered that this comparison would be useful given that entecavir is an alternative treatment to patients on tenofovir disoproxil for CHB.
- 8.9. The Committee noted the American Association for the Study of Liver Diseases (AASLD) guidelines (Terrault et al, Hepatology. 2018;67:1560-99 which recommends in cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or entecavir, taking into account any previously known drug resistance.
- 8.10. The Committee noted 'Study 108' (Buti et al. The Lancet Gastroenterology & Hepatology. 2016;1:196-206). The primary aim of this study was to confirm viral outcome related non-inferiority between TDF and TAF in a HBeAg negative population, the study achieved this aim. The members noted that this study consisted of predominantly Asian males, and that the two study groups were unbalanced at baseline with older patients in the TDF arm, potentially disadvantaging the TDF group with respect to the surrogate end-points reported for bone and renal function. Differences in creatinine clearance and bone mineral density at baseline were likely a reflection of this age unbalance. Further the members noted that the study specifically excluded patients with a creatinine clearance of 50 mL/min or less and excluded patients with significant renal or bone disease, the exact patient group of greatest interest with respect to the submission. Members noted the secondary outcomes with respect to bone and renal function in this study, and agreed that further long-term follow-up was required to confirm whether these results were clinically meaningful.
- 8.11. The Committee noted 'Study 110' (Chan, H et al. The Lancet Gastroenterology & Hepatology. 2016;1:185-95). The primary aim of this study was to confirm viral outcome non-inferiority between TDF and TAF in a HBeAg positive population, the study achieved this aim. As with Study 108, Study 110 specifically excluded patients with a creatinine clearance of 50 mL/min or less and excluded patients with significant renal or bone disease, the exact patient group of greatest interest with respect to the submission. Once again, members noted the secondary outcomes with respect to bone and renal function in this

study, and agreed that further long-term follow-up was required to confirm whether these results were clinically meaningful.

- 8.12. The Committee noted a poster presentation at an International Liver congress (Gane J. Hepatology 2018: 336) of a randomised controlled trial of TAF versus TDF in patients post liver transplant with stage 2 or more chronic kidney disease. Primary endpoints were maintenance of viral suppression at 24 weeks and secondary endpoints of hip and spine bone mineral density, creatinine, eGFR and direct GFR over 48 weeks. Members considered that the trial population was relevant to the submission, and would be interested to see the full trial results, when published, if the application were to be seen again. Members noted there was an early indication that viral suppression was maintained at week 12 with no significant changes in creatinine and glomerular filtration rates.
- 8.13. The Committee noted a number of other clinical trials that are due for completion between 2020 and 2023 which would be of interest (NCT0380619, NCT02862548, NCT03356834).
- 8.14. The Committee considered there is good evidence to demonstrate that TAF is non-inferior to TDF for virologic suppression. The Committee noted that in the case of renal impairment and osteoporosis there was limited data, as target population patients were excluded from the randomised controlled trials. Further, the Committee considered that the TAF benefits for renal and bone disease to date are surrogate markers that do not have good quality evidence to confirm the premium at which it is priced.
- 8.15. The Committee noted that this TAF has been considered by both the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the Canadian Drug Expert Committee (CADTH). Both of which provided a similar recommendation to this Committee.

## 9. Tenofovir alafenamide/emtricitabine in the treatment of HIV

### Application

- 9.1. The Committee reviewed the application for tenofovir alafenamide/emtricitabine in the treatment of HIV
- 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 tenofovir alafenamide/emtricitabine be listed as cost neutral to the currently funded pharmaceuticals containing tenofovir disoproxil in combination for the treatment of HIV.

### Discussion

- 9.4. The Committee noted that tenofovir alafenamide (TAF) is a novel nucleotide reverse transcriptase inhibitor (NRTI) that has demonstrated high antiviral efficacy at a dose less than one-tenth that of tenofovir disoproxil (TDF).
- 9.5. The Committee notes that this application was for TAF in combination with emtricitabine (FTC; TAF/FTC), the Committee considered that the application was based on a superiority in side effects profile compared to TDF/FTC due to higher concentration of active metabolite in cells and a corresponding lower plasma exposure resulting in a decrease in renal and bone toxicity. The Committee noted also that this application focused only on the benefits of TAF and therefore FTC is not discussed to any great degree.
- 9.6. The Committee noted the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) commentary on the US Department of Health and Human Services (DHHS) Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and

Adolescents (<http://arv.ashm.org.au/>). An antiretroviral therapy regimen for a treatment-naïve HIV-positive patient generally consists of two nucleoside/NRTIs, one of which is FTC or lamivudine (3TC), plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor with a pharmacokinetic enhancer. The Committee considered that the most commonly used NRTI backbone in New Zealand is TDF/FTC.

- 9.7. The Committee noted that in the ASHM commentary on the US DHHS 2018 guidelines a recommendation, than in chronic kidney disease, defined as creatinine clearance (CrCl) less than 60 mL/min, that TDF should be avoided and recommend abacavir (ABC) or TAF (if CrCl >30 mL/min). The commentary suggested other options where ABC or TAF cannot be used.
- 9.8. The Committee considered NRTI sparing regimens currently being explored in clinical trials and noted that dolutegravir (DTG) or raltegravir (RTG) containing dual therapy evidence is emerging and showing promise in renal impairment and multi-drug resistant HIV. The Committee noted that this information was not provided in the application.
- 9.9. The Committee considered Gemini I and II a non-inferiority study of DTG+3TC versus DTG+TDF/FTC in 719 and 722 HIV-1 treatment naïve adults. (Chan et al. abstract 13210 <http://programme.aids2018.org/Abstract/Abstract/13210>). Results indicate that as initial therapy, DTG+3TC was non-inferior to DTG+TDF/FTC at week 48. The trial also reported no treatment-emergent resistance, comparable activity in patients with HIV RNA greater than 100,000 and less effect on renal and bone markers. Members considered that this trial should be reviewed by the Anti-infective Subcommittee at its next meeting if the results are published.
- 9.10. The Committee provided background papers that studied chronic kidney disease in TDF treated patients as follows:
  - Quesada et al. *Int J Clin Pharm* 2015;37:865-72
  - Medland et al. *Int J STD AIDS* 2017;  
<https://doi.org/10.1177%2F0956462417722133>
  - Zachor et al. *AIDS* 2016;30:1221–8
  - Lewis et al. *J of Infection* 2017; 74:401-7
  - Mocroft et al. *Lancet HIV* 2016; 3:e501-2
  - Casado et al. *J AIDS* 2016;18: 59-68
  - Romo et al. *J AIDS Clin Res* 2014;5:pii-379
  - 9.10.1. In summary the Committee considered that overall the incidence of Fanconi syndrome is low, although it appears to be an idiosyncratic adverse event with TDF use in HIV. In patients that experience a reduction in eGFR many see subsequent improvement after switching or discontinuation of TDF.
- 9.11. The Committee provided background papers that studied osteoporosis in HIV patients as follows
  - Carr et al. 2015;16(suppl. 1):137-46
  - Bonjoch et al. *AIDS* 2010;24:2827-33
  - Escota et al. *AIDS Res Hum Retroviruses* 2016;32: 59-67
  - 9.11.1. Patients across the studies had heterogeneous baseline characteristics which may not be reflective of the New Zealand HIV patient population. It was noted

that HIV treatment in the modern era has witnessed patients living longer, starting treatment with normal bone mineral density, and overall achieving improved viral suppression and reduced risk of fractures.

9.12. The Committee considered study '1089' (Gallant et al. *Lancet HIV* 2016;3:e158-65 + Post et al. *HIV Clinical Trials* 2017;18:135-40 + Raffi et al. *J AIDS* 2017;75:226-31).

- This study, a non-inferiority design comparing TDF/FTC with TAF/FTC, was applicable to the New Zealand treatment setting. Enrolled patients were virologically suppressed for at least six months on TDF/FTC, had an eGFR greater than 50 mL/min, and were not on bisphosphonates. Patients received either 10 or 20 mg TAF/FTC depending on whether a protease inhibitor was provided.
- Members noted that females contributed a smaller number of the study participants.
- Members considered there were no differences in HIV-1 RNA, or CD4+ at 48 or 96 weeks. Thus non-inferiority was achieved. There was no difference between groups in fractures. Spine and hip bone mineral density had not reduced from baseline in either group.
- Members considered that at 48 weeks there were mean changes in serum creatinine, eGFR, and surrogate markers of renal tubular function which favoured TAF/FTC. However the long-term clinical benefit of this was uncertain.
- Members noted potential adverse lipid changes in the TAF arm.
- Members noted there were no discontinuations in the TAF/FTC group at 96 weeks due to adverse events, but there were two discontinuations in the TDF/FTC group due to hypertension and an increase in creatinine, and one laboratory finding consistent with proximal tubulopathy.

9.13. The Committee considered study '1717' (Winston et al. *Lancet HIV* 2018; pii: S2352-3018(18)30010-9. doi: 10.1016/S2352-3018(18)30010-9).

- This study, a non-inferiority design comparing ABC/3TC with TAF/FTC, was considered applicable to the New Zealand treatment setting. Enrolled patients were virologically suppressed for at least six months on ABC/3TC with eGFR greater than 50 mL/min, of note patients on bisphosphonates were excluded. Patients received either 10 or 20 mg TAF/FTC depending on if a protease inhibitor was provided.
- Members noted that once again the trial had a smaller proportion of females, however all baseline demographics appeared balanced.
- Members considered there were no differences in HIV-1 RNA, or CD4+ between groups at follow-up. Thus non-inferiority was achieved. At 48 weeks there was no difference between groups in spine and hip bone mineral density results.
- Members considered there were no clinically meaningful differences in renal results identified in the study.

9.14. The Committee considered study '104/111' (Sax et al. *Lancet* 2015; 385 (9987): 2606-15). This study compared TDF versus TAF in combination with elvitegravir, cobicistat and emtricitabine for treatment naïve HIV patients. TAF combination therapy showed less creatinine increases (0.08 vs 0.12 mg/dL;  $p < 0.0001$ ) proteinuria (median % change -3 vs 20;  $p < 0.0001$ ), spine and hip bone mineral density decreases (mean percentage change -

- 1.30 vs -2.86; -0.66 vs -2.95;  $p < 0.0001$ ). The Committee noted the decreases in bone mineral density and eGFR change from baseline plateaued after week 48 through to week 144.
- 9.15. The Committee considered study '109' (DeJesus et al. *AIDS Res Hum Retroviruses* 2018;34:337-42). In this study patients were virologically suppressed with one of four FTC/TDF regimes, patients were then randomised 2:1 to a TAF or TDF regime. Members considered there were no differences in viral suppression or fracture rates, there was one case of proximal tubulopathy in the TDF group and five (1%) discontinuations (vs. 2 (0.2%)) due to kidney adverse events. Concerns in lipid function over time were noted.
- 9.16. The Committee considered study '112' (Pozniak et al. *J Acquir Immune Defic Syndr*. 2016;71:530-7 and Post et al. Presented at the Conference of Retroviruses and Opportunistic Infections, February 22-25, 2016, Boston, MA) this was an open label study of treatment suppressed HIV patients with stable eGFR of 30-69 mL/min who were then switched to elvitegravir/cobicistat/FTC/TAF. The results show no change in eGFR out to 96 weeks.
- 9.17. After evaluating the evidence the Committee considered that in comparison with TDF, TAF, in patients with normal renal and bone disease, provides non-inferior viral suppression. TAF is associated with some advantage in surrogate markers for renal and bone outcomes, and some disadvantage in lipid markers, however the long-term clinical effect of these findings are currently uncertain. The committee noted that adverse renal and bone outcomes associated with TDF are often manageable and reversible. For patient with renal impairment there is limited data comparing TAF with alternatives including TDF; with many patients who might benefit being excluded from the studies. Osteoporosis patients had been excluded from the relevant RCTs.
- 9.18. The Committee considered that the evidence was of strong quality for the non-inferiority of TAF vs. TDF in the general HIV population. Members considered the evidence in renal disease was weak and very weak in bone disease.
- 9.19. The Committee noted that tenofovir alafenamide with emtricitabine has been considered by both the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the Canadian Drug Expert Committee (CADTH). Both of which provided a similar recommendation to this Committee.

## **10. Collagenase clostridium histolyticum in the treatment of Dupuytren contracture**

### Application

- 10.1. The committee reviewed the application for collagenase clostridium histolyticum in the treatment of Dupuytren contracture.
- 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 collagenase clostridium histolyticum be listed as cost-neutral to the average cost of managing Dupuytren contracture by surgical techniques.

### Discussion

- 10.4. The committee considered that, in most patients, Dupuytren contracture has a limited impact on a patient's health. The condition is not painful, but can cause some impediment to everyday activities.

- 10.5. The committee noted that more severe cases of Dupuytren contracture are treated with surgery, such as a fasciotomy, fasciectomy, or dermofasciectomy.
- 10.6. The committee noted that collagenase clostridium histolyticum (CCH) is a powder and liquid solution, which is reconstituted and injected into a palpable Dupuytren cord. CCH is registered with Medsafe which states it should only be done by qualified doctors who are experienced with Dupuytren disease, who are experienced in injecting into the hand, and who have undergone a training program run by the supplier. The committee noted that manipulation of the joint to break up the cord was required after each injection, and that one to three treatments may be needed.
- 10.7. The committee considered that some hand specialists have more experience with CCH than others, particularly those who been working overseas and have experience with it. Members considered that if funded, experience with CCH would improve with time. The committee noted that patients who receive a dose of CCH must return one or two days later to receive a follow-up manipulation, and that this should be done by the injecting doctor. Members considered that this could be a barrier to access as the injecting doctor may have limited availability, including only working certain days of the week.
- 10.8. The committee considered that the key evidence was from three studies, DUPY-303, CORD I, and CORD II, though DUPY-303 was a small study of 35 patients. Members considered that these trials provided reasonable quality evidence that CCH is better than placebo.
- 10.9. The Committee reviewed the evidence for CCH against other treatments. The committee noted the systematic reviews conducted by the applicant and a Health Technology assessment (Brazzelli M, et al Health Technol Assess. 2015;19:1-202). Members noted that Brazelli et al. stated there was no evidence that collagenase was better or worse than surgical treatments.
- 10.10. The committee also reviewed a matched study from the Netherlands comparing CCH against percutaneous needle aponeurotomy (PNA), which matched 130 patients and concluded the two approaches were similarly effective and safe. (Zhou C et al. *Plast Reconstr Surg Glob Open* 2017;5:e1425). The committee also reviewed an open-label, randomised controlled trial comparing CCH with percutaneous needle fasciotomy (PNF) in fifty patients which concluded that CCH “is not superior” to PNF and led to more complications. (Skov ST, et al. *J Hand Surg Am* 2017;42:321-8)
- 10.11. The Committee discussed evidence for recurrence rates of cords after each type of treatment. The committee noted that regardless of treatment, cords reoccur with time and further treatment becomes necessary. The Committee considered that the best evidence for recurrence with CCH came from the CORDLESS study. In that study, the cumulative 5-year recurrence rate was 47%, with 75% of occurrences occurring within 3 years of treatment. The committee noted that the NICE analysis (Brazelli et al.) had compared recurrence rates across treatment, and it concluded the 5-year recurrence rates to be 25.0% with limited fasciectomy, 42.8% with CCH (the lower limit of the 95% confidence interval from CORDLESS), and 52.5% with fasciotomy (PNF) (the midpoint of published estimates).
- 10.12. The committee reviewed a study considering retreatment with CCH after recurrence, which found rates of success were generally similar to those reported on initial CCH treatment. (Bear BJ, et al. *J Hand Surg Am* 2017;42:391.e1-8).
- 10.13. On adverse events of CCH, the committee reviewed a systematic review of 28 clinical studies and 5 case reports. (Sanjuan-Cerveró R, et al. *BioDrugs* 2017;31:105-15). It noted that peripheral edema, bruising, and upper limb pain were common adverse events. This event profile was largely relatively minor.

- 10.14. The Committee noted that in a pain study of 135 patients, the average numerical rating for pain (from 0 being no pain to 10 being the worst imaginable pain) during infiltration was 4.7. Pain was present before manipulation in 52.6% of patients. Pain from manipulation showed an average NRS score of 3.6 out of 10. (Sanjuan-Cerveró R, et al. J Hand Surg AmJ Hand Surg Am. 2017;42:e109-14).
- 10.15. Overall, the committee considered that CCH is probably equivalent in efficacy to fasciotomy in its initial response to treatment, and considered that CCH is probably not as good as fasciectomy. However, the committee also considered that the treatments had different relapse rates.
- 10.16. Members discussed whether to defer a decision until the results of a further comparison trial were available (DupuytrEn Treatment EffeCtiveness Trial (DETECT); Räsänen MP, et al. BMJ Open 2018;8:e019054. doi:10.1136/bmjopen-2017-019054). Overall, members considered that there was sufficient evidence of non-inferiority to make a recommendation now.
- 10.17. The committee considered that collagenase clostridium histolyticum should be funded only if it is cost-neutral to the average cost of management by surgical intervention. The committee considered that since a number of different surgeries are used, PHARMAC should research the relative use of each type to determine this average cost. The committee also considered that any calculation of costs should take into account recurrence rates of CCH versus surgery, and frequency of retreatment.
- 10.18. The committee suggested that PHARMAC contact the Middlemore Hand Surgery Unit for further information on the health need of patients with Dupuytren contracture and the relative effectiveness of the various treatments in the New Zealand context.

## 11. Etanercept – Biosimilar for use in all currently approved indications

### Application

- 11.1. The Committee reviewed a funding application from MSD, partnered with Samsung (Samsung Bioepis NZ Limited), for Etanercept – Biosimilar for use in all funded indications.
- 11.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Recommendation

- 11.3. The Committee **recommended** that, subject to Medsafe approval, MSD's etanercept (Brenzys) be listed on the Pharmaceutical Schedule only as cost saving compared to the currently listed etanercept reference product.
- 11.4. The Committee **recommended** that PHARMAC run a competitive process for the supply of etanercept and biosimilar etanercept for currently funded indications. The Committee recommended that any change be supported by a transition plan developed by PHARMAC staff.
- 11.5. The Committee **recommended** PHARMAC staff engage with relevant Subcommittees about biosimilar medicines being considered for funding.

### Discussion

- 11.6. The Committee noted this is the first biosimilar etanercept application to be considered by PTAC and that MSD's biosimilar etanercept (Brenzys) is not currently approved by Medsafe (approval expected in late 2018/early 2019). Members noted the application for MSD's biosimilar etanercept (Brenzys), a 50 mg prefilled syringe or autoinjector, requested equivalent funding to Pfizer's etanercept (Enbrel) for the treatment of indications currently

listed on the Pharmaceutical Schedule including: rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondyloarthritis, chronic plaque psoriasis, juvenile idiopathic arthritis, pyoderma gangrenosum, and adult-onset Still disease. Members noted some of these are unapproved indications.

- 11.7. The Committee noted that MSD's biosimilar etanercept (Brenzys) is approved in Australia, South Korea and Canada, and the same product, under the different brand name of Benepali, is approved by the European Medicines Agency (EMA) and widely used in Europe. Members noted the MSD biosimilar etanercept (Brenzys) 50mg is not likely to be approved in New Zealand for use in people under 18 years of age. The supplier noted a 25 mg strength Benepali product is available in Sweden and Denmark; however, MSD does not anticipate launching Brenzys 25 mg in New Zealand at this time. The Committee noted this could be problematic for patients requiring doses less than 50mg in New Zealand. Members noted the reference etanercept product (Enbrel) is available as 25mg prefilled syringe and autoinjector.
- 11.8. The Committee noted the currently funded etanercept , Enbrel (supplied by Pfizer), has been listed on the Pharmaceutical Schedule since 2003. Enbrel has subsidy and delisting protection until 30 June 2019, meaning that if a sole supply competitive process was undertaken, this could not start before 1 July 2019. Members noted current usage and expenditure for Enbrel.
- 11.9. Members reviewed the biosimilar etanercept (Brenzys) sample autoinjector device provided and noted the different mechanism to the reference product: the Brenzys autoinjector doesn't have a push button requiring the thumb to inject and therefore the user can activate the device by pressing the autoinjector onto the skin. Members considered this may be easier for patients with rheumatoid arthritis who often have affected hand joints.
- 11.10. The Committee noted the application was of good quality and well presented. The Committee noted the evidence provided is limited to one key study in adults with rheumatoid arthritis. Members noted the international regulatory requirements for biosimilar approval and indication extrapolation.
- 11.11. The Committee noted the primary evidence for efficacy, safety, tolerability, and immunogenicity of biosimilar etanercept (Brenzys) is provided by the Phase 3, randomised, double blind, parallel-group, SB4-G31-RA study which evaluated the biosimilar etanercept compared with EU (Europe) Enbrel in subjects with moderate to severe rheumatoid arthritis (NCT01895309; Emery et al. Ann Rheum Dis. 2017;76:51-7; Emery et al. Rheumatology (Oxford). 2017;56:2093-101). A total of 596 patients were randomly assigned 1:1 to receive Brenzys 50 mg (n = 299) or EU Enbrel 50 mg (n = 297) once weekly via self-administered subcutaneous injection using prefilled syringes. All patients received methotrexate 10-25 mg/week and folic acid 5-10 mg/week.
- 11.12. The Committee noted the proportion of patients achieving response at 24 weeks (defined by ACR20; American College of Rheumatology remission criteria) in the per-protocol set was 78.1% (193/247) in the biosimilar etanercept (Brenzys) group and 80.5% (190/236) in the EU Enbrel group (95% CI -9.41 to 4.98). Similar results were reported at 52 weeks. Further secondary outcomes using different clinical criteria tools (ACR50/70, DAS28 [Disease Activity Score based on 28 joints] and EULAR response criteria [European League Against Rheumatism]) were also comparable between biosimilar etanercept (Brenzys) and EU Enbrel groups, indicating that the efficacy was similar. The rate and type of adverse events were similar between products. The incidence of anti-drug antibodies (ADAs) up to week 52 was 1.0% (3/299) in the biosimilar etanercept (Brenzys) group and 13.2% (39/296) in the EU Enbrel group.
- 11.13. Members noted the open-label, 48-week extension of the SB4-G31-RA study, which included 245 patients who either continued to receive, or were switched to treatment with biosimilar etanercept (Brenzys). The results demonstrated that ACR responses and safety

were comparable between the Brenzys/Brenzys and EU Enbrel/Brenzys groups and were maintained from weeks 52 through to 100 (Emery et al. *Ann Rheum Dis.* 2017; doi: 10.1136/annrheumdis-2017-211591). Injection site reactions were lower in the Brenzys group (0.7% vs 5.7%;  $P < 0.001$ ). Overall safety information was comparable between Brenzys and Enbrel; however, members noted there was a small number of cancers reported, mostly in the Brenzys group, and one death was reported in the Brenzys group due to hepatic cancer that was considered related to the trial drug.

- 11.14. The Committee noted the approved indications for biosimilar etanercept (Brenzys) in other jurisdictions; Australia and the UK have funded biosimilar etanercept products alongside the Enbrel product. Members noted there are a number of observational studies based on European experiences of introducing biosimilar etanercept.
- 11.15. The Committee noted an abstract of the Danish DANBIO observational study (Glintbord B et al. *Arthritis Rheumatol* 2017;69(S10):1550) which reported 12 month clinical outcomes in 1623 patients with inflammatory arthritis who switched from Enbrel to biosimilar etanercept (SB4, Benepali). In patients who switched, 276 patients (18%) stopped SB4 treatment during follow-up, mainly due to lack of effect (54%) or adverse events (28%). Comparison of the withdrawal rate with a historic Enbrel treated patient cohort is ongoing and not yet available.
- 11.16. The Committee noted a New Zealand qualitative research study (funded by PHARMAC) regarding specialists' attitudes towards biosimilars (Hemington et al. [Pharmacoepidemiol Drug Saf.](#) 2017;26:570-7.). Members noted the study reflected that medical specialists held generally positive attitudes towards biosimilars but were less confident in indication extrapolation and switching patients. Members considered clinician acceptance of biosimilar medicines in New Zealand and internationally has grown significantly in recent years compared to when biosimilars were first available.
- 11.17. The Committee considered that based on the evidence it reviewed, MSD's biosimilar etanercept (Brenzys) demonstrated same or similar quality, safety and efficacy to etanercept (Enbrel) in adult patients. The Committee further considered that whilst there were no specific studies comparing MSD's etanercept (Brenzys) with Enbrel in other funded indications, there was no reason to consider that the two products would be any different in terms of quality, safety or efficacy in these settings.
- 11.18. The Committee considered that it would be appropriate for PHARMAC to run a Sole Supply process for etanercept for all indications currently funded, noting MSD's etanercept (Brenzys) may not be approved in New Zealand for use in people under 18 years of age. Members were concerned that the biosimilar etanercept (Brenzys) product did not address the health need of paediatric patients. The Committee considered that if biosimilar etanercept (Brenzys) was listed through a sole supply process, an appropriate alternative brand allowance would be required to address issues with supply to the paediatric market and also to manage any patients that could not tolerate the new product following a switch to biosimilar etanercept (Brenzys).
- 11.19. Members considered that patients could be switched from etanercept (Enbrel) to biosimilar etanercept (Brenzys); however, it was considered that implementation support would be important to ensure success of any change and PHARMAC would need to provide educational material to prescribers and patients to support such a switch if implemented. Members noted PHARMAC was in the process of developing implementation resources in this space and staff would provide an update to PTAC at a future meeting on this work. The Committee noted clinician input would be required to support any change to a biosimilar etanercept for patients and this could be a burden on clinicians.
- 11.20. The Committee noted that there are other biosimilar etanercept products available internationally and at least one other is undergoing evaluation by Medsafe. Members also noted the other TNF agents, adalimumab and infliximab, were also funded for the same or

similar indications and subject to the same or similar restrictions, and that biosimilar competition was also expected in these markets in the future.

- 11.21. The Committee advised that it would prefer to consider all biosimilar applications, however, this could occur following a commercial process if appropriate.
- 11.22. The Committee noted the MSD application also requested widened access for additional indications and an extended renewal period for Special Authority applications of 12 months, and that these considerations would be assessed by PHARMAC following commercial processes. The Committee noted undifferentiated spondyloarthritis was considered in 2015, at which time it recommended funding TNF inhibitors (adalimumab and etanercept) with a medium priority. This application has been ranked. Members noted no further clinical advice was required on this aspect of the application at this time.

## 12. Abatacept for the treatment of moderate to severe rheumatoid arthritis

### Application

- 12.1. The Committee reviewed the application for abatacept for the treatment of moderate to severe rheumatoid arthritis (RA).
- 12.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

### Recommendation

- 12.3. The Committee **recommended** that abatacept be listed only if cost-neutral to the least expensive biologic disease-modifying antirheumatic drug (bDMARD) currently funded for moderate to severe rheumatoid arthritis (RA).
- 12.4. The Committee recommended that the application for abatacept for the treatment of moderate to severe RA be referred to the Rheumatology Subcommittee of PTAC for advice regarding the place for abatacept in the RA treatment algorithm in New Zealand.

### Discussion

- 12.5. The Committee noted that estimates of the prevalence of RA in New Zealand vary from 0.46% to 2.8% depending on the case definition used ([Cross et al. Ann Rheum Dis. 2014;73:1316-22](#); Ministry of Health.2017. Annual Data Explorer 2016/17: New Zealand Health Survey [Data File]. URL: <https://minhealthnz.shinyapps.io/nz-health-survey-2016-17-annual-update/> [Accessed 10 August 2017]). The Committee considered that fewer than half of all patients diagnosed with RA will fit the criteria for moderate or severe disease.
- 12.6. The Committee noted the definition of moderate and severe RA characterized in the Global Burden of Disease 2010 study ([Cross et al. Ann Rheum Dis. 2014;73:1316-22](#)).
- 12.7. The Committee noted international management guidelines for RA, including those published by the American College of Rheumatology ([Singh et al. Arthritis Rheumatol. 2016;68:1-26](#)) and the National Institute for Health Care Excellence ([NICE guideline. Rheumatoid arthritis in adults: management. Published 11 July 2018](#)). The Committee noted that the aim of treatment for active RA is to achieve a target of remission or low disease activity if remission cannot be achieved ("treat-to-target").
- 12.8. The Committee noted that traditional disease-modifying antirheumatic drugs (DMARDs) include methotrexate (MTX), sulfasalazine, hydroxychloroquine, leflunomide, and intramuscular gold. The Committee noted that bDMARDs are initiated once a patient is not adequately responding to traditional DMARDs.

- 12.9. The Committee noted that there are five bDMARDs currently funded in New Zealand for the treatment of RA (subject to Special Authority criteria): etanercept, adalimumab, infliximab, rituximab, and tocilizumab.
- 12.10. The Committee noted that abatacept is a fusion protein produced by recombinant DNA technology that competes with CD28 for binding of CD80 and CD86, thereby interfering the T lymphocyte activation. The Committee noted that abatacept is the first of a novel class of bDMARDs known as selective costimulation modulators.
- 12.11. The Committee noted the findings of a Cochrane systematic review that concluded that the bDMARDs, including abatacept, are effective for the treatment of RA ([Singh et al. Cochrane Database Syst Rev. 2009;CD006848. doi: 10.1002/14651858.CD007848.pub2](#)). The Committee also noted the findings of a Cochrane systematic review which concluded that there is moderate-level evidence that abatacept is efficacious and safe for the treatment of RA ([Maxwell & Singh. Cochrane Database Syst Rev. 2009;7: CD007277. doi: 10.1002/14651858.CD007277.pub2](#)).
- 12.12. The Committee noted the single-blind, phase 3, non-inferiority AMPLE trial, that investigated the efficacy and safety of subcutaneous (SC) abatacept plus MTX compared with SC adalimumab plus MTX for the treatment of RA ([Weinblatt et al. Arthritis Rheum. 2013;65:28-38](#); [Schiff et al. Ann Rheum Dis. 2014;73:86-94](#)).
- 12.13. The Committee noted the eligibility criteria in the AMPLE trial: patients were required to have a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) of  $\geq 3.2$ , as well as a history of seropositivity for anti-cyclic citrullinated peptide antibodies or rheumatoid factor and/or an elevated erythrocyte sedimentation rate or C-reactive protein level.
- 12.14. The Committee noted the study design of the AMPLE trial: double-blinding for the study drugs was not feasible due to logistic barriers that did not permit masking of the syringes (patients were not blinded, Clinical assessors were blinded).
- 12.15. The Committee noted the 1-year results of the AMPLE trial ([Weinblatt et al. Arthritis Rheum. 2013;65:28-38](#)): of 646 patients who received treatment, 86.2% of patients in the abatacept group and 82.0% of patients in the adalimumab group completed 1 year of treatment. The Committee noted that the results of the primary efficacy analysis demonstrated that 64.8% of patients in the abatacept group and 63.4% of patients in the adalimumab group demonstrated an ACR20 response (difference 1.8%; 95% CI -5.6, 9.2), thus demonstrating noninferiority of abatacept compared with adalimumab. The Committee noted that the rate of serious adverse events (SAEs) was 10.1% in the abatacept group compared with 9.1% in the adalimumab group, the rate of serious infections was 2.2% compared with 2.7%, and the rate of injection site reactions was 3.8% in the abatacept group compared with 9.1% in the adalimumab group ( $P=0.006$ ).
- 12.16. The Committee noted the 2-year results of the AMPLE trial ([Schiff et al. Ann Rheum Dis. 2014;73:86-94](#)): 79.2% of patients in the abatacept group and 74.7% of patients in the adalimumab group completed two years of treatment. The Committee noted that the efficacy outcomes remained comparable between groups and with the year one results. The Committee considered that there was a similar rate of adverse events (AEs) and SAEs between the treatment groups; but noted that the rate of serious infections was 3.8% in the abatacept group and 5.8% in the adalimumab group, and that there were fewer discontinuations due to AEs, SAEs, and serious infections in the abatacept group. The Committee also noted that the rate of injection site reactions was 4.1% in the abatacept group compared with 10.4% in the adalimumab group.
- 12.17. The Committee considered that abatacept has a different mechanism of action compared with the other funded bDMARDs and may therefore provide an alternative option for patients who do not respond to other therapies.

- 12.18. The Committee considered that the evidence provided by the AMPLE trial was of moderate quality, and adequately demonstrated the noninferiority of abatacept compared with the key funded comparator, adalimumab.
- 12.19. The Committee considered that it remains unclear if there is a need for an additional bDMARD option in the RA treatment landscape, and therefore requested that the application for abatacept be reviewed by the Rheumatology Subcommittee of PTAC to consider its place in the RA treatment algorithm.