

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 3 & 4 May 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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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Present:

PTAC members:

Mark Weatherall (Chair)
Alan Fraser
Jennifer Martin
Marius Rademaker
Matthew Strother
Sean Hanna
Stephen Munn
Tim Stokes

1. Subcommittee Minutes

Haematology Subcommittee

- 1.1. The Committee noted the complete record of the Haematology Subcommittee meeting held on 4 October 2017.
- 1.2. The Committee noted the Subcommittee recommendations 6.3 and 6.4 regarding ruxolitinib. The Committee noted the Subcommittee had recommended ruxolitinib be funded for the treatment of high risk and intermediate-2 risk myelofibrosis with a high priority and for the treatment of symptomatic intermediate-1 risk myelofibrosis with a medium priority. The Committee noted this differed from their recommendations made in November 2016 which were medium and low respectively.
- 1.3. The Committee noted the Subcommittee's view that there was considerable unmet health need and that withdrawal syndrome would be manageable. The Committee considered that as no new evidence for efficacy was raised by the Subcommittee, it was appropriate to retain its previous recommendations.
- 1.4. The Committee reiterated its recommendations that ruxolitinib for the treatment of high risk and intermediate-2 risk myelofibrosis, be funded with a **medium** priority and that ruxolitinib for the treatment of intermediate-1 risk myelofibrosis, be funded with a **low** priority.
- 1.5. The Committee noted the Subcommittee advice (5.23) that there was no ongoing need for danaparoid to remain listed. The Committee noted a potential rare use for heparin-induced thrombocytopenia induced Budd–Chiari syndrome post-liver transplant, but that this was a rare situation and may only occur in one to two patients per year in New Zealand.
- 1.6. The Committee noted and accepted the remainder of the minutes of the October 2017 Haematology Subcommittee meeting.

Anti-Infective Subcommittee

- 1.7. The Committee noted the complete record of the Anti-infective Subcommittee meeting held on 2 November 2017.
- 1.8. The Committee noted that PTAC had, at its February 2018 meeting, reviewed the partial draft record of the Anti-Infective Subcommittee meeting held on 2 November

2017, covering the Subcommittee's discussion on pre-exposure prophylaxis (PrEP) for prevention of HIV.

- 1.9. The Committee noted PHARMAC's intent to review the criteria for PrEP approximately 12 months after listing. The Committee considered that there are significant issues with patient access to named prescribers and that this should not be a barrier to treatment. The Committee recommended that Special Authority applications for PrEP should be changed from 'named prescribers' (currently Anti-retroviral prescribers) to 'sexual health and infectious disease physicians'.
- 1.10. The Committee noted paragraphs 3.1, 3.11 and 4.20, which included recommendations to restrict particular antibiotics to specific patient groups or indications for anti-microbial stewardship reasons. Members noted that these recommended restrictions were not for reasons of cost, but intended to limit the harm from antimicrobial resistance, as encompassed by the Factors for Consideration. The Committee considered that there are three potential options available to PHARMAC to implement these recommendations, being endorsement, Special Authority and education (educational materials and activities). Members considered that while endorsement/special authority tools are not particularly effective for low cost medicines, they do place additional prompts for prescribers to carefully consider their prescribing decisions.
- 1.11. The Committee noted paragraph 4.17 regarding making cefalexin available on a Practitioner Supply Order (PSO). The Committee considered that this was not appropriate for this antibiotic and further that the argument supporting the change could be made for the emergency use of any pharmaceutical. The Committee considered that if a patient were so unwell that they could not wait until the next morning to fill an antibiotics prescription then it may be more appropriate that they should be referred immediately to hospital for acute parenteral treatment.

Special Foods Subcommittee

- 1.12. The Committee noted the complete record of the Special Foods Subcommittee meeting held on 2 December 2017.
- 1.13. The Committee noted paragraph 5.3 regarding the recommendation to change food thickeners Special Authority applicants to neurologists. Members considered that this was too narrow a prescriber group and that this prescriber group would not see many of the patients who would be treated under this Special Authority. Members recommended that 'Relevant Specialists' would be more appropriate.
- 1.14. The Committee noted paragraph 10.11 recommending the listing of Alfamino where a cost neutral or cost saving and a high priority was given. Members considered both recommendations are not logical and recommended that Alfamino should be listed if cost neutral or cost saving to the Combined Pharmaceutical Budget.
- 1.15. The Committee noted paragraph 11.2 regarding the recommendation to list Advital in the Schedule with a high priority for patients with taste fatigue. Members considered that the definition of taste fatigue should be brought to this Committee. PTAC would like to review the proposed Special Authority that defines taste fatigue as there are large potential patient groups and a high chance of slippage.

2. Correspondence & Matters Arising

Adalimumab audit results

- 2.1. The Committee noted the findings of an audit of adalimumab Special Authorities.

Golimumab for the treatment of ulcerative colitis – correspondence

- 2.2. The committee reviewed correspondence from the original applicant and supplier of golimumab. The committee noted they would also be reviewing an application for adalimumab for ulcerative colitis this meeting.
- 2.3. The committee noted a new open-label, uncontrolled retrospective cohort study of 142 patients (Taxonera et al Inflamm Bowel Dis 2017;0:1–9). The committee noted the results reported by the trial, but commented that open-label audit-type studies generally report better results than randomised controlled trials.
- 2.4. The committee noted a new paper describing maintenance use of golimumab by Gibson et al (Clinical and Translational Gastroenterology, 2016;7:e168). The committee considered this paper showed that patients who respond well initially would continue to respond.
- 2.5. The committee noted there are a number of agents for the treatment of ulcerative colitis from pharmaceutical classes other than TNF α -inhibitors that are currently available or that may be suitable for funding applications in the near future. The committee considered it would be valuable to consider an overall picture on all such agents once each was reviewed individually.
- 2.6. The committee considered that the correspondence did not provide sufficient reason to change its previous recommendation. The committee reiterated its previous **recommendation** that the application for the funding of golimumab for the treatment of moderate to severe ulcerative colitis be **declined**.

Trinomia for the treatment of secondary prevention of cardiovascular disease – correspondence

- 2.7. The committee reviewed correspondence from the applicant and supplier of Trinomia, Te Arai BioFarma.
- 2.8. Members discussed their concerns about over-prescription for people at low risk of cardiovascular disease. Members also noted that polypills such as Trinomia also have an issue in relation to adverse events, where if an event occurs it is difficult to know which component may be causing it, making dose titration of the components more difficult.
- 2.9. The committee considered that the correspondence did not provide reason to alter its previous recommendation on Trinomia. It reiterated its previous **recommendation** that the application for aspirin, atorvastatin, and ramipril combination pills be **declined**.

Establishment of the Rare Disorder Subcommittee

- 2.10. The Committee noted an update from PHARMAC staff on the work that is underway in the area of rare disorders. It noted that PHARMAC will establish a Rare Disorders Subcommittee of PTAC and that PTAC members had been approached to sit on the Subcommittee.

3. Levofloxacin for the treatment of helicobacter pylori

Application

- 3.1. The committee reviewed the levofloxacin for the second line treatment of H. pylori.
- 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 levofloxacin be listed with a **high priority** for second-line treatment eradication of proven *H. pylori* infection when co-administered with a proton pump inhibitor and amoxicillin, if bismuth products are unavailable.
- 3.4. The Committee considered that the Anti-infective Subcommittee should be made aware of this review and the above recommendation.
- 3.5. The Committee **recommended** that all *H. pylori* eradication treatments in New Zealand should be for 14 days based on evidence of eradication rates. Members considered that the Special Authority for clarithromycin should be changed to reflect this.

Information Reviewed

- 3.6. The application with all documentation provided by the applicant
- 3.7. The following additional information:
 - [BPACnz. The changing face of H pylori testing](#). Best Tests. 2014 May 23:20-25
 - [Yuan et al. \(2013\) Optimum duration of regimens for Helicobacter pylori eradication](#).
 - [Cochrane Database Syst Rev 12:CD008337](#)
 - [Wu et al. \(2014\) Evidence-based recommendations for successful Helicobacter pylori treatment](#). Expert Rev Gastroenterol Hepatol 8:21–28
 - [Graham et al. \(2014\) Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence](#). Clin Gastroenterol Hepatol 12:177–186.e3; discussion e12–e13
 - [Kim et al. \(2015\) Sequential or concomitant therapy for eradication of H. pylori infection: a systematic review and meta-analysis](#). Gastroenterol Hepatol 30:1338–1345
 - [Gisbert et al. \(2015\) Helicobacter pylori second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments](#). Aliment Pharmacol Ther 41:768–775
 - [Cochrane Database Syst Rev. 2015 Jul 22;\(7\)](#)
 - [BPACnz. Antimicrobial resistance: where are we now?](#) Ikram, Rosemary (2010) Best Practice J. 33:33-37
 - [BPACnz. Quinolone antibiotics - limit use](#) Ikram, Rosemary (2011) Best Practice J. 32-37

Discussion

- 3.8. The Committee considered an application to list levofloxacin for second-line therapy for *Helicobacter pylori* (*H. pylori*) eradication. Members noted that the application had been reviewed by the Anti-infective Subcommittee and the Gastrointestinal Subcommittee. Members noted that the Anti-infective Subcommittee had recommended the application be declined on the basis that they wanted to see more information on a number of issues including New Zealand resistance rates to current treatments and fluoroquinolones.
- 3.9. The Committee considered that bismuth is a well-established and effective treatment for *H. pylori* eradication. Bismuth is not an antibiotic but is used with metronidazole based therapies to kill organisms that are potentially resistant to metronidazole therapy. The Committee noted the supply issues with bismuth, and considered that PHARMAC should make its best efforts to continue to source bismuth for this use and

considers that for good antimicrobial stewardship it is worth ensuring continued supply.

- 3.10. The Committee considered a prospective cohort study of *H. pylori* eradication. (Taguchi H et al. *Medicine (Baltimore)*. 2017;96:e9507.) The study examined the improvement in quality of life and epigastric symptoms, evaluated before and after the eradication of *H. pylori*. These outcomes were measured using the 8-item Short-Form Health Survey (SF-8) and the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease, respectively. In the indices of quality of life on the SF-8, the scores on both the mental component summary (MCS) and the physical component summary (PCS) were found to have significantly improved after the eradication of *Helicobacter pylori*. Members noted that no actual figures were given, and the study made no mention of Minimally Important Clinical Difference (MICD), so members considered it difficult to know whether these were clinically relevant, but the improvements were the same irrespective of the treatment regimen used.
- 3.11. The Committee considered that there are a large number of treatment regimens for this infection: Standard triple therapy is 7-14 days of a proton pump inhibitor and two antibiotics. There are also 5-day sequential regimens, 7- and 14 day quadruple regimens with bismuth and other concomitant regimens and levofloxacin based regimens. Members noted that treatment names can be abbreviated with the letters denoting the medicine used: PAL = proton pump inhibitor, amoxicillin and levofloxacin. PBMT = proton pump inhibitor, bismuth, metronidazole and tetracycline. PAC = proton pump inhibitor, amoxicillin and clarithromycin.
- 3.12. The Committee noted a meta-analysis of randomised controlled trials considering proton pump inhibitor treatment regimens showing a significantly greater proportion of eradication with longer durations compared with shorter durations (ITT: 45 studies, 14 vs 7 days, 82% vs 73%; 12 studies, 14 vs 10 days, 84% vs 79%). (Yuan Y, et al. *Cochrane Database Syst Rev* 2013;12:CD008337).
- 3.13. The Committee considered in the second-line setting, a meta-analysis of five studies assessed PAL after failure of sequential non-bismuth quadruple therapy that yielded an overall eradication rate of 81% (95% CI, 71%–91%). Marin AC et al. *Expert Opin Pharmacother* 2013;14:843–61. Another meta-analysis reported an eradication success rate with PAL of 81% after sequential (6 studies) and 78% after concomitant (3 studies) non-bismuth quadruple therapy. Marin AC, et al. *Helicobacter* 2014;19(suppl 1):139–40. Meta-analyses of studies comparing PAL and PBMT as second-line therapy reported no statistically significant differences in overall eradication rates (77%–79% with PAL vs 67%–69% with PBMT). Di Caro S, et al. *World J Gastroenterol* 2012;18:5669–78.
- 3.14. The Committee considered one randomised controlled trial which reported 14-day PAL to be as effective as 14-day PBMT in patients for whom 7-day triple therapy had failed (ITT eradication rates of 86.3% and 86%, respectively). Chuah SK, et al. *Helicobacter* 2012; 17:374–81. However, a recent non-randomised unblinded ‘real-world’ retrospective cohort study reported superior performance of PBMT over PAL in second to sixth-line rescue therapy (ITT, 84% vs 61%; RD, 24% [95% CI, 10%–37%]). (Shaikh T et al. *Can J Gastroenterol Hepatol*. 2016;2016:7321574). Eradication rates were significantly higher (88.7%; 95% CI, 56.1%–100%; $P < .05$) with 10-day compared with 7-day levofloxacin-containing regimens (70.6%; 95% CI, 40.2%–99.1%). (Di Caro S, et al. *World J Gastroenterol* 2012;18:5669–78)
- 3.15. The Committee considered that there is no data in New Zealand specifically for *H. pylori* resistance rates to levofloxacin. The Committee considered available

published data identified for New Zealand for resistance rates for gram-negative enteric bacteria (*H. pylori* included) for any fluoroquinolones in general (levofloxacin included). This was confined to laboratory surveillance data relating to ciprofloxacin resistance in *Campylobacter jejuni*, where 15.5% (46) of 297 *C. jejuni* isolates surveyed were ciprofloxacin resistant.

- 3.16. Members considered that there is limited data from a New Zealand study of 73 patients that showed a resistance rate for *H. pylori* of 16.4% for clarithromycin, 49.3% for metronidazole, and 9.5% for moxifloxacin (Hsiang et al N Z Med J. 2013 Oct 18;126(1384):64-76.). The Committee considered that the prevalence of resistance of levofloxacin would likely be similar to that reported for moxifloxacin.
- 3.17. The committee noted an open-label Australian study of 150 patients that treated patients with esomeprazole 40 mg, amoxicillin 1g, or levofloxacin 500mg, each twice daily (Katelaris PH [Intern Med J. 2017;47:761](#)). Members considered this study showed an eradication rate (ITT) of 90%, with mild adverse effects in 11% of patients, and no levofloxacin resistance in 20 cases tested. However, the committee also noted that fluoroquinolone resistance increased as more fluoroquinolones were more widely prescribed.
- 3.18. The Committee considered that, given the supply issues with bismuth, levofloxacin should be funded with high priority for second-line treatment eradication of proven *H. pylori* infection if bismuth is unavailable.
- 3.19. The Committee considered that the Anti-infective Subcommittee should be made aware of the review of this application by this committee and the recommendation that was made, particularly noting that it had considered New Zealand specific data where possible.

4. Oral viscous budesonide for the treatment of eosinophilic oesophagitis

Application

- 4.1. The committee reviewed the application for oral viscous budesonide for the treatment of eosinophilic oesophagitis.
- 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 oral viscous budesonide be listed with a **medium priority** for proven eosinophilic oesophagitis with dysphagia in patients not responsive to first line steroids, with applications to be made by a gastroenterologist or on the recommendation of a gastroenterologist.

Information Reviewed

- 4.4. The application with all documentation provided by the applicant
- 4.5. The following additional information:
 - [Prasad et al. Clin Gastroenterol Hepatol. 2009,7 \(10\):1055-61](#)
 - [Aceves et al. Am J Gastroenterol. 2007,102 \(10\):2271-9](#)
 - Albert et al. Dig Dis Sci 2016;61:1996-2001
 - Murali et al. J Gastroenterol Hepatol. 2016;31:1111-9

Discussion

- 4.6. The Committee noted that an application had been made by two separate applicants to fund budesonide ampoules for the treatment of eosinophilic oesophagitis. The Committee noted that the Gastrointestinal Subcommittee had recommended declining funding in adults and had given a high priority recommendation in children. The Committee also noted that at its meeting of November 2017 it asked to review the evidence itself before making a final recommendation.
- 4.7. The Committee considered that, currently, paediatric and adult patients with eosinophilic oesophagitis are clinically managed in the same way, namely first-line treatment with proton pump inhibitors and, if this is not successful, 6-food elimination diet for 8-12 weeks is usually tried for paediatric patients but has limited acceptance from adult patients. Swallowed inhaled corticosteroids and mechanical dilation of the oesophagitis are next steps if proton pump inhibitor therapy and dietary treatment are ineffective.
- 4.8. The Committee considered there is significant health need of patients with eosinophilic oesophagitis. The Committee also noted that both children and adults can have significant symptoms affecting swallowing, food impaction and vomiting. The Committee considered that children have difficulty with current therapy which requires use of a meter dose inhaler but coordinating breathing to swallow the dose instead of inhaling it. The Committee noted that this problem for children does not appear to be an issue for most adult patients.
- 4.9. The Committee noted there is no commercial oral viscous preparation of budesonide available internationally and that currently the nebule formulation is compounded into a viscous solution. The Committee noted that if budesonide nebules were listed, there would still be a cost for the compounding elements, such as a sucralose-based artificial sweetener like Splenda. The Committee considered that patients or carers would self-fund the compounding agents and mix the nebules with the Splenda (or equivalent) themselves on the direction of the prescriber. Members noted that if a pharmacist was required to compound this product, it would result in a significant part charge for the patient.
- 4.10. The Committee considered patient numbers estimated by an applicant and the Gastrointestinal Subcommittee. Members noted the large increase in eosinophilic oesophagitis diagnosis rates in New Zealand and considered that this is consistent with international trends. Members considered that there are likely to be 200-300 or more new cases per year in New Zealand with eosinophilic oesophagitis although the future prevalence is difficult to estimate if incidence rates are rapidly increasing.
- 4.11. The committee reviewed a randomised controlled trial comparing oral nebulised budesonide against placebo in 36 patients (Straumann et al. Gut 2010;59:21–30.). The committee considered that while this was not a viscous formulation, it provided evidence that budesonide was effective in treating eosinophilic esophagitis in both adults and adolescents.
- 4.12. The committee reviewed two randomised controlled trial comparing oral viscous budesonide against placebo in 93 patients and 32 patients respectively (Dellon et al. Gastroenterology 2017,152:776-786) (Dohil et al. Gastroenterology 2010,139:418-429). The committee also reviewed a meta-analysis and systematic review by Murali et al (2016) which included those two studies and three more, for a total of 174 patients with eosinophilic oesophagitis treated with topical steroids. Both topical fluticasone and viscous budesonide significantly improved histology (decrease in

eosinophil count). There was a trend towards improvement in clinical symptoms with topical steroids, compared to placebo, whereas budesonide treatment showed a statistically significant improvement in symptoms. Members commented that the treatment does not work when strictures are present and that dilatation is sometimes required.

- 4.13. Overall, the committee considered that there was sufficient evidence to support the use of oral viscous budesonide in this indication for both children and adults. Members considered that initial approval could be twice daily for 6 weeks, then renewals could perhaps be for up to 2-4 years.

5. Immune checkpoint inhibitors for advanced urothelial carcinoma

Application

- 5.1. The Committee reviewed applications from Merck Sharp & Dohme NZ Limited for pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing therapy (first-line treatment) and for patients after failure of a platinum-containing chemotherapy regimen (second-line treatment).
- 5.2. The Committee reviewed a funding application from Roche Products NZ for atezolizumab for the treatment of patients with locally advanced or metastatic UC following progression on platinum-containing chemotherapy (second-line treatment)

Recommendation

- 5.3. The Committee **recommended** pembrolizumab for the first-line treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing therapy be **declined** based on the poor strength and quality of currently available evidence.
- 5.4. The Committee **recommended** pembrolizumab be funded with **low priority** for the second-line treatment of locally advanced or metastatic UC after failure of a platinum-containing chemotherapy regimen.
- 5.5. The Committee **recommended** that atezolizumab be listed with **low priority** for the second-line treatment of locally advanced or metastatic UC following progression on platinum-containing chemotherapy.
- 5.6. The Committee **recommended** that the applications for pembrolizumab and atezolizumab as second-line UC treatment be **referred** to the Cancer Treatment Subcommittee for advice regarding appropriate access criteria, population size, current UC patient management and further consideration of a class effect.
- 5.7. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Information Reviewed

- 5.8. The application with all documentation provided by the applicant along with the additional information detailed in the discussion.

Discussion

- 5.9. The Committee noted that the estimated incidence of bladder cancer in New Zealand is approximately 5.1 per 100,000 population with a total of 420 registered diagnoses

in 2015, of which 6% were in Māori patients. The Committee noted that UC is the most common type (around 90%) of bladder cancer.

- 5.10. The Committee noted that approximately a quarter of UC patients are diagnosed with metastatic disease or will eventually develop metastatic disease.
- 5.11. The Committee noted that New Zealand data indicate that the 5-year survival rates for patients with localised, regional, or distant UC are 78.6%, 35.1%, and 4.9%, respectively.
- 5.12. The Committee noted that the current first-line treatment for patients with locally advanced or metastatic disease is cisplatin-based combination chemotherapy (gemcitabine and cisplatin; methotrexate, vinblastine, doxorubicin, and cisplatin). The most commonly utilised second-line therapy in New Zealand are taxanes (paclitaxel or docetaxel).
- 5.13. The Committee noted that New Zealand patients who are ineligible for cisplatin-based chemotherapy, generally due to poor performance status or renal impairment, are likely to receive alternative chemotherapy regimens (gemcitabine and carboplatin, paclitaxel and gemcitabine, or docetaxel and gemcitabine).

Pembrolizumab first-line treatment

- 5.14. The Committee noted that the key clinical evidence provided for the use of pembrolizumab as first-line therapy for cisplatin-ineligible patients with locally advanced or metastatic UC comes from a single-arm, non-randomised Phase 2 cohort study in 370 patients with advanced and unresectable or metastatic UC of the renal pelvis, ureter, bladder, or urethra to received pembrolizumab 200 mg every 3 weeks until disease progression or unacceptable toxicity (KEYNOTE-052, [Balar AV, et al. *Lancet Oncol.* 2017;18:1483-92](#)).
- 5.15. The Committee noted that cisplatin-ineligibility was defined as meeting at least one of the following criteria: ECOG performance status 2, creatinine clearance 30-60 ml/min, grade ≥ 2 audiometric hearing loss, grade ≥ 2 peripheral neuropathy, or New York Heart Association Class III heart failure).
- 5.16. The Committee noted that, according to the Medsafe Data Sheet, cisplatin is contraindicated in patients with serum creatinine levels greater than 0.2 mmol/L rather than described in terms of eGFR. The Committee considered that many UC patients, including those with renal impairment which is relatively common in UC, are currently treated with carboplatin regimens. The Committee considered that if eligibility were determined by cisplatin ineligibility it would be important for this to be appropriately defined in any access criteria and that there may be differing clinical interpretations of any definition in terms of intolerance and contraindication.
- 5.17. The Committee noted that the median age of patients in the KEYNOTE-052 trial was 74 years, 77% were male, 42% had an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2 , and 10% had previously received adjuvant or neoadjuvant platinum-based chemotherapy.
- 5.18. The Committee noted the median duration of treatment was 3 months and the median duration of follow-up was 5 months. A total of 89 (24%) patients had an objective response. The median progression-free survival (PFS) was 2 months. The 6-month PFS rate was 30% and the 6-month overall survival (OS) rate was 67%.
- 5.19. The Committee noted that the efficacy and safety of pembrolizumab in this indication is being further assessed in the randomised, open-label, Phase 3 KEYNOTE-361 trial ([NCT02853305](#); currently recruiting, estimated completion data June 2019).

- 5.20. The Committee considered there was limited weak evidence of poor-to-moderate quality coming from a single phase 2 non-randomised cohort study to support the efficacy of pembrolizumab as first-line therapy for cisplatin-ineligible patients with advanced UC.
- 5.21. The Committee considered that based on currently available evidence in a first-line setting there was insufficient data to determine what, if any, clinical effect pembrolizumab had as a first line treatment of cisplatin ineligible advanced UC. The Committee considered that it was not appropriate to extrapolate data from a second-line setting, particularly when additional data would be available in the near future.
- 5.22. The Committee considered that the supplier's cost-effectiveness modelling was highly optimistic and had significantly overestimated the cost effectiveness of pembrolizumab as a first line advanced UC treatment.

Pembrolizumab second-line treatment

- 5.23. The Committee noted that the key clinical evidence for the use of pembrolizumab as second-line treatment for advanced UC comes from KEYNOTE-045 a randomised, open-label, Phase 3 trial in 542 patients with advanced UC of the renal pelvis, ureter, bladder, or urethra, that had recurred or progressed after platinum-based chemotherapy to receive pembrolizumab 200 mg or investigator's choice of chemotherapy (paclitaxel 175 mg/m²; docetaxel 75 mg/m²; vinflunine 320 mg/m²) every 3 weeks until disease progression or unacceptable toxicity ([Bellmunt J, et al. *N Engl J Med.* 2017;376:1015-26](#)).
- 5.24. The Committee noted that in KEYNOTE-045 the median age of patients was approximately 66 years, 74% were male, the majority had an ECOG performance status of 0 or 1 (98%), and 34% had liver metastases. The Committee noted median duration of treatment was 3.5 months in the pembrolizumab arm and 1.5 months in the chemotherapy arm.
- 5.25. The Committee noted that at a median follow-up of 14.1 months, the median OS was 10.3 months in the pembrolizumab arm compared with 7.4 months in the chemotherapy arm (HR for death 0.73; 95% CI 0.59-0.91; *P*=0.002). The Committee noted estimated 12-month OS rate was 43.9% in the pembrolizumab arm compared with 30.7% in the chemotherapy arm; median PFS was 2.1 months in the pembrolizumab arm and 3.3 months in the chemotherapy arm; and the estimated 12-month PFS rate was 16.8% and 6.2% in the pembrolizumab and chemotherapy arms respectively.
- 5.26. The Committee noted that health-related quality of life (QoL) data from the KEYNOTE-045 trial were presented at the 2017 Genitourinary Cancers Symposium ([Vaughn DJ, et al. *J Clin Oncol.* 2017;35 \(suppl\) 28](#)). The Committee noted that from baseline to Week 15, global health status/QoL scores were stable for patients in the pembrolizumab arm but worsened for patients in the chemotherapy arm (difference in Least Squares 9.05; 95% CI 4.61-13.48; nominal 2-sided *P*<0.001).
- 5.27. The Committee noted that updated 2-year follow-up data from the KEYNOTE-045 trial after a median follow-up of 27.7 months were presented at the 2018 Genitourinary Cancers Symposium ([Bellmunt J, et al. *J Clin Oncol.* 2018; 36: \(suppl\) 41](#)) indicating a median OS of 10.3 months in the pembrolizumab arm and 7.3 months in the chemotherapy arm (HR 0.70; *P*<0.0002).
- 5.28. The Committee considered that paclitaxel and docetaxel are appropriate comparators for the New Zealand population, but that vinflunine is not registered in New Zealand. It

was noted that in the KEYNOTE-045 trial, 168 of the 255 treated patients in the chemotherapy arm received paclitaxel or docetaxel.

- 5.29. The Committee considered there was currently limited evidence from a single open label RCT for the benefits of pembrolizumab in the treatment of second-line advanced UC. The Committee considered that from currently available evidence while it appeared there were marginal quality of life and survival benefit from pembrolizumab in a population with poor survival gains with standard chemotherapy options the magnitude was unclear.
- 5.30. The Committee considered that from the evidence provided it appeared that PD-L1 status was not relevant in determining the advanced UC patient population who may benefit from pembrolizumab either in a first or second-line setting.

Atezolizumab second-line treatment

- 5.31. The Committee noted that the key clinical evidence for the use of atezolizumab as second-line therapy in advanced UC comes from the IMvigor211 trial; a randomised, open-label, Phase 3 trial in 931 patients with metastatic UC who had progressed after platinum-based chemotherapy were randomly assigned 1:1 to receive atezolizumab 1200 mg or investigator's choice of chemotherapy (vinflunine 320 mg/m²; paclitaxel 175 mg/m²; or docetaxel 75 mg/m²) every 3 weeks until disease progression or unacceptable toxicity ([Powles T, et al. *Lancet*. 2018;391:748-57](#)).
- 5.32. The Committee noted that the median age was 67 years, 77% were male, and 100% of patients had an ECOG performance status of 0 or 1. The Committee noted that the median duration of treatment was 2.8 months in the atezolizumab arm and approximately 1.9 months in the chemotherapy arm.
- 5.33. The Committee noted that at a median follow-up of 17.3 months, median OS in the intention-to-treat (ITT) population was 8.6 months in the atezolizumab arm compared with 8.0 months in the chemotherapy arm (stratified HR 0.85; 95% CI 0.73-0.99; and 12-month OS rate in the ITT population was 39.2% in the atezolizumab arm and 32.4% in the chemotherapy arm).
- 5.34. The Committee noted that the primary analysis was conducted in patients with ≥5% PD-L1 expression in tumour-infiltrating immune cells; and that in this subgroup the median OS did not differ significantly between the atezolizumab and chemotherapy arms (11.1 months vs 10.6 months [HR 0.87; 95% CI 0.63-1.21; *P*=0.42]). The Committee considered that while this analysis demonstrated no difference in efficacy in this population, there was some evidence of a survival benefit in the ITT population. The Committee noted that the supplier had stated that the survival with vinflunine was better than hypothesized in the IMvigor211 trial which may have compromised the statistical assumptions used in the trial.
- 5.35. The Committee considered that paclitaxel and docetaxel are appropriate comparators for the New Zealand population, but that vinflunine is not registered in New Zealand. It was noted that in the IMvigor211 trial, 201 of the 443 treated patients in the chemotherapy arm received paclitaxel or docetaxel.
- 5.36. The Committee considered that based on the graphical representation of quality life data provided there did not appear to be evidence of a short-term quality of life benefit in the atezolizumab study population and it was unclear if there was a longer term benefit.
- 5.37. The Committee noted evidence for the use of atezolizumab in advanced UC from a single arm phase 2 cohort study ([Rosenburg et al. *Lancet* 2016;387:1909-20](#)).

- 5.38. The Committee considered that there was currently limited evidence of a survival benefit from a single open label RCT for the benefits of atezolizumab in the treatment of second-line advanced UC, and considered it was uncertain whether longer-term data published from the IMvigor211 trial would be published.
- 5.39. The Committee considered that from the evidence provided it appeared that PD-L1 status was not relevant in determining the advanced UC patient population who may benefit from atezolizumab.

General Discussion

- 5.40. The Committee considered that if any checkpoint inhibitor were funded for the second-line treatment of advanced UC following progression on platinum-based chemotherapy, given the adverse event profile of platinum agents it was likely patients may receive abbreviated first-line treatment in order to progress to the checkpoint inhibitor.
- 5.41. The Committee considered that based on currently available evidence, the adverse event profile for pembrolizumab and atezolizumab in UC was comparable to that seen with melanoma or NSCLC populations.
- 5.42. The Committee considered that based on currently available evidence pembrolizumab and atezolizumab have an equivalent therapeutic effect in the second-line treatment of advanced UC. The Committee considered that the difference between the results of KEYNOTE-045 and IMvigor211 could primarily be attributed to differing trial design and analysis methods; which presented difficulties in comparisons for the data from these trials. The Committee considered there was greater uncertainty regarding the likely benefits from pembrolizumab as compared to atezolizumab for patients with advanced UC due to the trial design for KEYNOTE-045.
- 5.43. The Committee noted that, while nivolumab is not currently registered in New Zealand for use in UC, the results of the single-arm Phase 2 Checkmate 275 trial of nivolumab in patients with metastatic or surgically unresectable UC who have progressed or recurred despite previous platinum-based chemotherapy have been published ([Sharma P, et al. *Lancet Oncol.* 2017;18:312-22](#)). The Committee considered based on the data from this trial it was likely that nivolumab would provide similar benefits for advanced UC patients and further supported a class effect for PD-1/PD-L1–targeted immune checkpoint inhibitors in the second-line treatment of advanced UC following platinum-containing therapy.
- 5.44. The Committee noted that there appeared to be other immune checkpoint inhibitors also under investigation for the treatment of advanced UC.
- 5.45. The Committee considered that if pembrolizumab or atezolizumab were funded as second-line therapy for advanced UC it may replace taxanes for some patients, however, most patients would likely receive a taxane as third-line therapy.

6. Pembrolizumab for the treatment of Hodgkin’s Lymphoma

Application

- 6.1. The Committee reviewed the application for pembrolizumab for the treatment of classical Hodgkin Lymphoma (cHL) which has relapsed after two lines of chemotherapy and is either ineligible for or relapsed following an autologous stem cell transplant (ASCT).

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

Recommendations

- 6.3. The Committee **recommended** that the application for pembrolizumab for the treatment of classical Hodgkin Lymphoma (cHL) which has relapsed after two lines of chemotherapy and is either ineligible for or relapsed following an autologous stem cell transplant (ASCT) be **deferred** until the updated evidence for brentuximab vedotin published since the last PTAC consideration is reviewed by Cancer Treatment Subcommittee of PTAC.
- 6.4. The Committee **recommended** that the application for pembrolizumab for the treatment of classical Hodgkin Lymphoma (cHL) which has relapsed after two lines of chemotherapy and is either ineligible for or relapsed following an autologous stem cell transplant (ASCT) be **referred** to the Cancer Treatment Subcommittee of PTAC, with their view sought on the health benefits of pembrolizumab and brentuximab vedotin in this setting, clarity in the treatment sequencing and the role of alloSCT if pembrolizumab were funded and provide advice on special authority (SA) criteria.

Information Reviewed

- 6.5. The application with all documentation provided by the applicant along with the additional information detailed in the discussion.

Discussion

- 6.6. The Committee noted there are around 100 new cases per year of classical Hodgkin Lymphoma (cHL) in NZ, and in general, the patients are relatively young and have good outcomes despite not having brentuximab vedotin which is the current standard of care in other countries, with an overall survival rate at 5 years of about 80%. The Committee noted that about 20-25 patients per annum would fall into the group of patients classified as having relapsed or refractory disease (RR cHL) and of those patients it was reasonable to expect about 50% would respond well to autologous stem cell transplant (ASCT), leaving about 10 patients per year eligible for pembrolizumab.
- 6.7. The Committee noted the evidence for a health benefit of ASCT in RR cHL is poor. The Committee noted by way of example that OS was not significantly different in a RCT by Schmitz et al ([Lancet. 2002;359:2065-71](#)).
- 6.8. Some evidence that alloHCT does provide a survival advantage but treatment-related morbidity and mortality is high. Graft versus host disease (GVHD) may be more common after checkpoint inhibitor use. If alloHCT is an important component of treatment for RRHL then the costs of this, including matched-unrelated donor alloHCT need to be included in any cost-utility analysis (it was included in the supplier submission CUA)
- 6.9. The Committee noted that internationally these patients would likely be treated with brentuximab vedotin. The Committee noted it had in August 2016 considered a clinician application for brentuximab vedotin for the treatment of Hodgkin Lymphoma but had recommended decline for the majority of the indications applied for given their view that the evidence was of generally of poor strength and quality, and lacking overall survival data.
- 6.10. The Committee noted the NICE guidance in development. The Committee considered that the paper by Cheah et al ([Ann Oncol. 2016;27:1317-23](#)) included in the

application was regarded by NICE as the best available evidence to demonstrate outcomes prior to the use of newer investigational agents. The Committee agreed that this was useful given that the majority of patients (71/100) had prior ASCT, but not truly representative of the New Zealand population given brentuximab vedotin was not funded here. The committee noted a significant number of included patients were treated with investigational agents including a very small number who received immune checkpoint inhibitors.

- 6.11. The Committee also noted ([Arai et al. *Leuk Lymphoma*. 2013;54:2531-3](#) and [Bair et al. *Am J Hematol*. 2017;92:879-8](#)) were useful in determining likely current outcomes in New Zealand in RR cHL patients. The Committee noted those with RR cHL have poor outcomes, especially if brentuximab vedotin is not available, with a median OS of around 2.4 years from the time of the ASCT. With brentuximab vedotin treatment, outcomes are improved with median OS of around 7 years. Once relapse occurs whilst on, or soon after, brentuximab vedotin treatment, outcomes are again poor with median OS of about 2 years. The Committee considered that this new information since that last PTAC consideration which is significant and also affects the place in therapy for pembrolizumab.
- 6.12. The Committee noted the non-comparative studies Armand et al. *J Clin Oncol*. 2016;34:3733-39 (KEYNOTE 013) and Chen et al. *J Clin Oncol*. 2017;35:2125-32 (KEYNOTE 087). The Committee noted fixed pembrolizumab dosing of 200 mg every three weeks was used in KEYNOTE 087 resulted in a much lower average total dose per person (12.6g vs 2.6g). The Committee noted there were no significant differences between three cohorts in KEYNOTE 087 in terms of response rates and there was low rate of discontinuation due to adverse events (4.3%). The Committee noted the 9-month PFS and OS were 63.4% and 97.5% respectively. The Committee considered these results appear superior to those depicted in Cheah et al. The Committee considered weaknesses of the data to include that there is no comparator arm, the follow-up times are short and relevance to the NZ context is more difficult to establish as brentuximab vedotin is not currently available or used.
- 6.13. The Committee noted four published non-comparative studies of nivolumab in RR cHL ([Ansell et al. *N Engl J Med*. 2015;372:311-9](#); [Armand et al. *J Clin Oncol*. 2018;36:1428-39](#); [Beköz et al. *Ann Oncol*. 2017;28:2496-502](#); [Herrera et al. *Blood*. 2018;131:1183-94](#)) which show similar PFS and OS trends to those seen for pembrolizumab and thus also superior to those depicted in the Cheah et al study (*Ann Oncol*. 2016;27:1317-23). The Committee considered the nivolumab studies are also weak for the same reasons as the pembrolizumab evidence but noted that there were two cohorts of patients not exposed to brentuximab vedotin, possibly making these more relevant to the New Zealand population.
- 6.14. The Committee noted there are a number of additional studies underway for pembrolizumab and nivolumab in RR cHL including a phase 3 trials for each agent versus brentuximab and a number of phase 1/2 trials in combination with salvage chemotherapy, immunodulatory agents, other immune checkpoint inhibitors and cell-targeted therapies.
- 6.15. The Committee noted that given brentuximab vedotin is not currently available in New Zealand, the efficacy, cost-effectiveness and tolerability of pembrolizumab versus current treatment may be higher. The Committee noted that if pembrolizumab was to be funded for RR cHL, infusions would be required every 3 weeks for an average of 13 treatments. The Committee noted this may result in more RR cHL patients

receiving alloSCTs, with GVHD possibly resulting in significant incremental costs, but CaTSOP's view should be sought on this point.

- 6.16. The Committee also noted the combination of a checkpoint inhibitor with brentuximab vedotin may have merit in brentuximab vedotin naive RR cHL patients ([Herrera et al. Blood. 2018;131:1183-94](#)).
- 6.17. The Committee noted that the supplier had recognised in their submission that the data presented in support of this funding application is not of the usual strength required and were willing to discuss pricing that is predicated on the results of KEYNOTE-204 (which is powered to demonstrate superiority of pembrolizumab over brentuximab vedotin in both PFS and OS). The Committee considered that the applicability of the results of KEYNOTE 204 are too uncertain, especially when New Zealand doesn't yet fund brentuximab vedotin.
- 6.18. The Committee considered that it was very likely that brentuximab vedotin, pembrolizumab and nivolumab all provide a health benefit compared to the current treatments for RR cHL despite the poor quality of evidence available at this stage. The Committee considered there was new evidence for brentuximab vedotin since the last PTAC consideration and it was important that CaTSOP's view be sought on that data considering its relevance to this funding application.

7. Liraglutide for the treatment of Type 2 Diabetes

Application

- 7.1. The Committee reviewed the application for liraglutide for the treatment of type two diabetes mellitus (T2DM) in light of new information about the effect of liraglutide on cardiovascular outcomes.
- 7.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendations

- 7.3. The Committee **recommended** that liraglutide be funded with a **high priority** for patients with T2DM with established high cardiovascular risk, noting the importance of appropriately defining this population.
- 7.4. The Committee **recommended** that the application be **referred** to the Diabetes Subcommittee for advice regarding appropriate access criteria, including definition of a high cardiovascular risk population, and updated advice regarding the diabetes treatment paradigm in light of evidence for cardiovascular effects with some agents.

Information Reviewed

- 7.5. The application with all documentation provided by the applicant along with the additional information detailed in the discussion.

Discussion

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

- 7.7. The Committee noted that applications for antidiabetic agents have been reviewed by PTAC and the Diabetes Subcommittee individually and together on a number of occasions. The Committee noted that overall, PTAC had previously concluded that these agents were generally similar in the treatment of T2DM, in terms of reducing glycated haemoglobin (HbA1c) by approximately 0.5% to 1%, but that there has been a lack of evidence supporting clinically significant benefits other than decreased HbA1c (which is but an intermediate outcome). The Committee noted that its previous recommendations were for funding for each agent with a low priority. The Committee noted that none of these agents were currently funded in New Zealand.
- 7.8. The Committee noted that in November 2017 PTAC had considered additional published evidence for the use of empagliflozin and recommended funding with a high priority for the treatment of patients with T2DM with established high cardiovascular risk, noting the importance of appropriately defining this population. The Committee noted the application was also referred to the Diabetes Subcommittee for advice on appropriate access criteria including definition of a high cardiovascular risk population.
- 7.9. The Committee noted that additional information had been provided by the supplier of liraglutide including published evidence for its effect on cardiovascular (CV) outcomes in patients with T2DM from the randomised, double-blind, placebo-controlled, non-inferiority Phase 3 LEADER trial ([Marso SP, et al. *N Engl J Med.* 2016;375:311-22](#)).
- 7.10. The Committee noted that in the LEADER trial, 9340 patients with T2DM, an HbA1c $\geq 7.0\%$, and high CV risk (age ≥ 50 years with ≥ 1 CV coexisting condition, or age ≥ 60 years with ≥ 1 CV risk factor), were randomly assigned 1:1 to receive liraglutide 1.8 mg or matching placebo once daily as a subcutaneous injection in addition to standard of care.
- 7.11. The Committee noted that median time of exposure to liraglutide or placebo in the LEADER trial was 3.5 years and the median follow-up was 3.8 years in each treatment group.
- 7.12. The Committee noted that 81.3% of participants had established cardiovascular disease 72.4%, chronic kidney disease of stage 3 or higher 24.7%, or both 15.8%; at baseline, the mean duration of diabetes was 12.8 years, and the mean HbA1c was 8.7%.
- 7.13. The Committee noted that time to first occurrence of death from cardiovascular causes, (nonfatal (including silent) myocardial infarction, or nonfatal stroke), the primary composite outcome, occurred in 13.0% of patients in the liraglutide group compared to 14.9% in the placebo group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority).
- 7.14. The Committee noted that the rate of death from any cause was 8.2% in the liraglutide group compared to 9.6% in the placebo group (HR, 0.85; 95% CI, 0.74 to 0.97; $P = 0.02$); and rate of CV mortality was 4.7% compared to 6.0% in the liraglutide and placebo groups respectively (HR, 0.78; 95% CI, 0.66 to 0.93; $P = 0.007$).
- 7.15. The Committee noted that the authors conclude that the number of patients who would need to be treated to prevent one event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause. However, as liraglutide was taken in addition to antihypertensive treatment, the Committee considered that a more appropriate measure of the incremental gain from liraglutide

- would be that one Major Adverse Cardiovascular Event (MACE) is prevented for every 200 patient years of treatment.
- 7.16. The Committee noted that a number of health technology appraisal bodies internationally have assessed the efficacy of liraglutide for the treatment of patients with T2DM; and considered that the recommendations differed in part due to varied comparators in each country.
 - 7.17. The Committee noted that as liraglutide is a subcutaneous injection preparation it is likely that some patients would find administration less preferable to an oral agent; and because of this if liraglutide were funded uptake may be lower than would be expected if a new oral agent was funded.
 - 7.18. The Committee considered that use of liraglutide would likely result in a reduction in the need for blood glucose testing and sulphonylureas however, there was no direct evidence to support this.
 - 7.19. The Committee considered that if funded liraglutide would likely be used as an add-on therapy in combination with other funded anti-diabetic agents (oral agents and/or insulin). The Committee did not consider the funding of liraglutide would influence the rate patients progress from oral anti-diabetic agents alone to addition of insulin.
 - 7.20. The Committee considered that it was important to appropriately define a high CV risk population based on trial evidence but this needs to be balanced with the practicalities for its implementation in New Zealand. Members considered advice from cardiologists may be useful when determining access criteria for a high CV risk population.
 - 7.21. The Committee noted that a recently published study which reviewed the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on CV risk factors ([Dalsgaard NB, et al. *Diabetes Obes Metab.* 2018;20:508-19](#)). The Committee considered that this review was limited to surrogate CVD markers (blood pressure, heart rate, body weight, lipid profile, and glycaemic control) and did not include any publications that investigated long-term CVD outcomes. The Committee noted that the authors considered GLP-1 receptor agonists appeared to have diverse effects on CV risk factors which may vary depending on agent characteristics, including short-acting compared to continuous-acting and small and large molecules.
 - 7.22. The Committee noted a meta-analysis which examined the efficacy of GLP-1 receptor agonists compared with placebo with respect to CV outcomes ([Bethel MA, et al. *Lancet Diabetes Endocrinol.* 2018;6:105-13](#)). The Committee noted that GLP-1 receptor agonist treatment showed a 10% relative risk reduction in the composite CV endpoint (CV mortality, non-fatal myocardial infarction, and non-fatal stroke) compared with placebo HR 0.90 (95% CI 0.82-0.99); and a 12% relative risk reduction in all-cause mortality compared with placebo HR 0.88 (95% CI 0.81-0.95). The Committee considered that the mortality risk reductions were of a similar level in published evidence of individual studies and that this analysis did not directly address whether there was evidence for a class effect in terms of CV outcomes for GLP-1 receptor agonist therapy except in the sense of a failure to identify statistical heterogeneity in the pooled analysis.
 - 7.23. The Committee noted a network meta-analysis that aimed to evaluate the relative efficacy of treatment intensification with liraglutide compared with sodium glucose cotransporter 2 (SGLT-2) inhibitors in the absence of head-to-head randomised controlled trials ([Lorenzi M, et al. *Diabetes Ther.* 2017;8:85-99](#)). The Committee considered that results of Lorenzi et al. indicated that liraglutide was statistically superior to SGLT-2 inhibitors with respect to change from baseline in HbA1C and free

plasma glucose, and the odds of reaching an HbA1C target of <7%. The Committee considered that SGLT-2 inhibitors appeared to have a similar impact on weight reduction and risk of hypoglycaemia. The Committee noted that the date of the literature search was October 2014, which was prior to the publication of the LEADER trial.

- 7.24. The Committee noted a systematic review and meta-analysis conducted to compare the effects of SGLT-2 inhibitors, GLP-1 agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors on mortality and CV endpoints in patients with T2DM ([Zheng SL, et al. JAMA. 2018;319:1580-91](#)). The Committee considered the results indicated that both SGLT-2 inhibitors and GLP-1 agonists were associated with a reduction in all-cause and CV mortality compared with the control groups; and DPP-4 inhibitors were not associated with a reduction in mortality.
- 7.25. The Committee considered that in the absence of head to head trials, in terms of CV outcomes, GLP-1s and SGLT-2s may have a similar class effect. However, the Committee considered that, based on the currently available evidence, different agents may provide different effects on CV disease and diabetes risk factors for example in terms of renal outcomes, blood pressure and heart rate.

8. Adalimumab for the treatment of ulcerative colitis

Application

- 8.1.1. The Committee reviewed the application for adalimumab for the treatment of moderate to severely active ulcerative colitis.

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

Recommendations

- 8.3. The Committee **recommended** that the adalimumab be listed for treatment of ulcerative colitis as a second-line biologic treatment in patients who were non-responders to infliximab with a **low priority**.
- 8.4. The Committee **recommended** that the application for adalimumab for first biologic line treatment of ulcerative colitis be **deferred** until PHARMAC staff report back to PTAC on the availability of infliximab in each DHB.

Information Reviewed

- 8.5. The application with all documentation provided by the applicant
- 8.6. The following additional information:
- Prior minutes relating to adalimumab for the treatment of moderate to severely active ulcerative colitis from PTAC and Subcommittees
 - Four-Year Maintenance Treatment With Adalimumab in Patients with Moderately to Severely Active Ulcerative Colitis: Data from ULTRA 1, 2, and 3

Discussion

- 8.7. The Committee noted this was a resubmission made in 2017 following a PTAC recommendation to decline in 2014, and noted that this resubmission had already been reviewed by the Gastrointestinal Subcommittee.

- 8.8. The Committee noted that the prevalence of ulcerative colitis was increasing across the world, and that multiple treatments had been developed. The Committee noted that adalimumab is a subcutaneous injection that patients can self-administer, while infliximab requires an infusion in a medical facility, and considered that having a subcutaneous treatment available would improve access to treatment.
- 8.9. The Committee considered ULTRA-3, (Colombel et al. Am J Gastroenterology 2015;109:1771-1780) an open-label maintenance extension study of 199 patients from the previously considered studies ULTRA-1 and ULTRA-2. Members had concerns about the patient group definition and patient selection; it considered it was difficult to fully determine how patients were selected and could not find baseline patient characteristics at the time of enrolment in ULTRA-3. The Committee considered that given the elaborate design and the heterogeneous set of patients, it was uncertain if the patient group studied in ULTRA-3 was subject to selection bias (and thus not representative of the original trials), or how this might affect the generalizability of the reported findings to New Zealand patients.
- 8.10. The Committee considered a meta-analysis by Danese et al (Annals Internal Med 2014;160:704-711) which combined seven double-blind, placebo-controlled trials in biologic-naive patients of adalimumab, infliximab, golimumab, and vedolizumab. The Committee considered this review to be of good quality. The Committee considered that it showed all agents to have benefits, and that infliximab was probably the more effective of the four agents.
- 8.11. The Committee noted Christensen et al. 2015 (Scan J Gastroenterol 2015;50:1018-24) which studied patients taking adalimumab after infliximab was unsuitable. It was a retrospective study of 33 patients. It concluded that efficacy of adalimumab in this patient group was modest in clinical practice.
- 8.12. The Committee considered that the evidence shows that infliximab is likely to provide better health outcomes than adalimumab when used as a first-line biologic agent to treat ulcerative colitis. The committee felt it was provided with limited evidence in support of second-line use in non-responders. The best data comes from ULTRA-2. At Week 8, the difference in clinical remission rates between the adalimumab and placebo arms was significant among patients who had never been exposed to infliximab (21% vs 11%; $P=.017$). In contrast, the difference in clinical remission rates between the adalimumab and placebo arms at Week 8 in patients who had been exposed to infliximab did not reach statistical significance (9% vs 7%; $P=.559$). At Week 52, differences in clinical remission between the active treatment and placebo arms reached statistical significance in relation to both infliximab-naive patients (22% vs 12%; $P=.029$) and infliximab-experienced patients (10% vs 3%; $P=.039$).
- 8.13. The Committee considered a study by Burmester et al (Annals of the Rheumatic Diseases 2013;72:517-524) which reported adalimumab's adverse event rates from a number of studies. The Committee noted that infections were the most common event. The Committee considered that the new data showed better safety and tolerability than was shown by the previously reviewed evidence.
- 8.14. The Committee noted the applicant's estimate that, if funded as a first biologic line, about 30 patients would be on adalimumab for ulcerative colitis in the first year, rising to 300 on treatment by year 5. The Committee considered that the actual impact if funded would likely be higher than that. The Committee considered it did not have enough information to estimate impact if funding was restricted to second biologic line. Members considered that if funded, adalimumab would be used at different

places in the treatment algorithm for different patients, not exclusively used as a first-line, or exclusively used as a later line.

- 8.15. Members discussed what treatment might be used after failure of both infliximab and adalimumab, as members noted a 40% non-response rate in ULTRA-3. Members considered that vedolizumab was also an effective agent in treating ulcerative colitis which had gained significant market share in Australia, but noted it was not Medsafe-registered, or funded in New Zealand.
- 8.16. The Committee considered that infliximab is the appropriate comparator, but also considered that it may not be available in all DHBs. Members noted that while infliximab is listed in Section H, this does not require a DHB to provide it. Members considered that where infliximab is not available, funding adalimumab as first biologic line would be of benefit but if infliximab is available, then it would be of less value. Members expressed concern at inequitable access to medicines if infliximab were not equally available throughout the country.
- 8.17. The Committee considered that listing adalimumab as an additional biologic option for treating ulcerative colitis would provide improved health benefits, but considered that infliximab had better efficacy, so recommended that adalimumab be funded with a low priority for patients who were non-responders to infliximab. The Committee also considered that, since infliximab may not be available in all DHBs, adalimumab may be appropriate as a first biologic line, so deferred making a recommendation at first biologic line until PHARMAC staff report back to PTAC on the availability of infliximab in each DHB.

9. Ustekinumab for the treatment of severe Crohn's disease

Application

- 9.1. The Committee reviewed the application for ustekinumab for the treatment of Crohn's disease.
- 9.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendations

- 9.3. The Committee **recommended** that ustekinumab be listed for Crohn's disease, in patients where a TNF inhibitor has failed, with a medium priority.

Information Reviewed

- 9.4. The application with all documentation provided by the applicant
- 9.5. The following additional information:

- [Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease](#)

Discussion

- 9.6. The Committee noted that ustekinumab is an anti IL12/23 biologic agent, unlike adalimumab and infliximab which are TNF- α inhibitors. The Committee considered that while ustekinumab would be used in combination with regular non-biologic agents, it would not be used in combination with other biologics. The Committee noted that the initial loading dose of ustekinumab is administered as an intravenous infusion but that subsequent doses were via subcutaneous injection. Members noted that the patient group under consideration were patients with severe Crohn's disease,

- namely those that initially qualified for infliximab or adalimumab but who had not received an initial response or lost the response with time. Members considered that this patient group had high health needs and a lack of suitable alternative treatments.
- 9.7. The Committee considered that the key clinical trials were the UNITI-1, UNITI-2, and IM-UNITI trials (all described in Feagan et al NEJM 2016;375:1946-60). The Committee also considered the GETAID study (Wils et al 2018. 2018,47:588-595) which provided real-world data.
 - 9.8. Members noted that the trials showed high response rates in placebo arms, and noted that practical secondary measures such as change in CRP and fecal calprotectin were low in placebo arms. Members considered this related to the use of CDAI as the primary outcome. Members noted, for example, that 36% of patients in the maintenance placebo arm maintained a 'response'. Members considered that Crohn's Disease Activity Index (CDAI) is an older measure of Crohn's disease activity that can be influenced by non-inflammatory symptoms and includes psychological measures in its score. Members also considered that using CDAI as a score system may cause issues in getting a homogenous group at the start of the trial. In this study the higher than usually expected maintenance of remission in the placebo group may represent a prolonged effect of the initial loading dose.
 - 9.9. The Committee considered that the trials were of high quality, with adequate statistical power and generalizability, and that from these trials it was clear that ustekinumab has biological activity. Members considered that in general the difference in success rates between ustekinumab and placebo was moderate. Members considered the evidence showed ustekinumab was modestly effective in treating Crohn's disease, but was less effective in patients for whom a TNF α -inhibitor had failed than for TNF α -inhibitor-naive patients.
 - 9.10. Members discussed the response rates in patients with prior TNF-inhibitor α . The Committee discussed the evidence comparing ustekinumab with adalimumab in treating Crohn disease, noting that the CHARM study was the pivotal study for adalimumab (Colombel et al (2007) Gastroenterology Jan;132(1)52-65). The Committee noted there are no direct comparisons of ustekinumab with other agents. However the Committee considered that ustekinumab was probably not as effective as adalimumab.
 - 9.11. Members considered that funding ustekinumab following failed anti-TNF treatment may lead to a reduction in hospital admissions and the need for surgery but there was no data on this.
 - 9.12. Members discussed other treatment options for Crohn's disease, including an alternative option of adalimumab rescue therapy in which adalimumab is given weekly. Members asked if this increased dose would be more cost-effective than giving a new agent. Members discussed the value in optimising the use of currently listed therapies, and discussed if funding adalimumab rescue dosing should be reconsidered now that the price has decreased. Members noted that another biologic agent, secukinumab, an IL-17 inhibitor, does not appear to be effective in treating Crohn's disease.
 - 9.13. The Committee considered that given the evidence suggesting that ustekinumab was not as effective as adalimumab, it should recommend ustekinumab for Crohn's disease at second biologic line, after the trial of an anti-TNF α agent, with a medium priority.

10. Pirfenidone for widening access to for the treatment of idiopathic pulmonary fibrosis.

Application

- 10.1. The Committee considered the recommendations of the respiratory subcommittee to amend the special authority criteria of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF).

Recommendations

- 10.2. The Committee **recommended** that the special authority criteria for pirfenidone be amended by increasing the upper FVC limit to 90% predicted, and for IPF to be diagnosed by a multi-disciplinary team, with a **high priority**.
- 10.3. The Committee **recommended** that the pirfenidone stopping criteria should not be amended at the current time, until robust and higher quality evidence is available.

Discussion

- 10.4. The Committee reviewed recommendations of the August 2017 Respiratory Subcommittee related to a proposal to widen access to pirfenidone for the treatment of idiopathic pulmonary fibrosis. The Committee reviewed the correspondence from clinicians, the supplier, relevant trials related to this proposal, and the recommendations and analysis from several overseas jurisdictions.
- 10.5. The Committee noted that the evidence to support widened access to pirfenidone is from a series of pooled data from trials previously considered in the initial recommendation to fund pirfenidone.
- 10.6. The Committee noted that the evidence used to support a widened entry criteria predominantly came from Albera et al. 2016 (Eur Respir J. 2016;48:843-51). This was a post-hoc analysis using pooled data from 1247 patients who were randomized to pirfenidone 2403 mg or placebo in the CAPACITY (PIPF-004 and PIPF-006) and ASCENT (PIPF-016) trials, stratified to determine the benefits of pirfenidone when used in patients with FVC $\geq 80\%$ vs $< 80\%$ predicted. The Committee noted approximately 25% of patients in the analysis had a FVC $\geq 80\%$. The Committee considered that this was likely due to the inclusion criteria to both the CAPACITY and ASCENT trials which required patients to have FVC of between 50-90%. The Committee noted that of those patients who had FVC $\geq 80\%$, the average FVC was 89% in both the pirfenidone and treatment groups.
- 10.7. The Committee noted that patients treated with pirfenidone in both the FVC $\geq 80\%$ and $< 80\%$ groups were statistically less likely to experience a $\geq 10\%$ decline in in FVC or death over 12 months compared to patients who received placebo. Patients treated with pirfenidone in the FVC $< 80\%$ subgroup were also less likely to experience a ≥ 50 meter decline in 6MWD (6 minute walk distance) or death compared with placebo-treated patients, however this did not reach statistical significance in patients with baseline FVC $\geq 80\%$. The Committee also noted that patients with FVC $\geq 80\%$ who were treated with pirfenidone did not differ significantly from placebo-treated patients in terms of reports of shortness of breath made using the UCSD SOBQ (University of California San Diego Shortness of Breath Questionnaire).
- 10.8. The Committee noted the high health need of patients with IPF, and considered that the above evidence suggests that there is a benefit to being treated with pirfenidone earlier. The Committee noted the inclusion criteria of the phase III trials, and

considered that from the evidence available, the Special Authority for pirfenidone should be amended to match the FVC range used in those trials.

- 10.9. The Committee noted Nathan et al. (Thorax 2016;71:429-35), a pooled analysis using data from the 1247 patients in the phase III CAPACITY (PIPF-004 and PIPF-006) and ASCENT (PIPF-016) trials, to determine the benefits of continued treatment with pirfenidone versus placebo in patients who have already had a $\geq 10\%$ decline in FVC.
- 10.10. The Committee noted that the study analysed the proportion of patients on pirfenidone or placebo who had a $\geq 10\%$ decline in FVC in the first three and six months of treatment, who then experienced a subsequent $\geq 10\%$ decline in FVC or died. The Subcommittee noted that the subgroup who continued treatment with pirfenidone had a lower risk of subsequent FVC decline or death compared to those patients who continued with placebo (5.9% vs 27.9% respectively, $p < 0.009$). The Committee noted that the authors concluded that ongoing treatment with pirfenidone after an initial $\geq 10\%$ decline in FVC resulted in a lower subsequent risk of FVC decline or death as compared with placebo.
- 10.11. The Committee noted the methodology employed in the Nathan et al. study, and considered that there was no clear direct comparison of pirfenidone versus placebo in patients who experienced a $\geq 10\%$ initial decline in FVC. The Committee noted that patients who were previously treated with pirfenidone, continued treatment with pirfenidone after the initial $\geq 10\%$ decline in FVC, and patients previously treated with placebo continued on placebo, and that the analysis then compared the difference in the rates of decline in these groups. The Committee noted that the trial design meant that the two arms were effectively different population groups, and considered that it cannot be distinguished whether the effects observed were from a sustained response to prior treatment with pirfenidone, or whether the benefits were from the on-going use of pirfenidone after the initial $\geq 10\%$ decline in FVC, or whether there was another explanation for the difference observed. The Committee considered that the data at this time remains inconclusive about the benefits of ongoing treatment with pirfenidone after $\geq 10\%$ decline in FVC. The Committee recommended that the stopping rule should remain in the current Special Authority criteria for pirfenidone, until there is more evidence available.
- 10.12. The Committee noted the wording of the IPF diagnosis criterion currently used in the NZ criteria for pirfenidone, which states 'Patient has been diagnosed with idiopathic pulmonary fibrosis as confirmed by histology, CT or biopsy'. The Committee noted the risks associated with lung biopsies, and considered that biopsies are seldom conducted for the diagnosis of IPF. The Committee considered that this criterion should be amended and reworded so that diagnosis is made via a multi-disciplinary team (MDT) including a radiologist. The Committee noted that smaller centres around New Zealand may not have access to a full MDT, however considered that regular teleconferences of these centres with larger tertiary centres would ensure that patients with suspected IPF are discussed.

11. Mepolizumab for the treatment of severe Eosinophilic Refractory Asthma

Application

- 11.1. The Committee considered the recommendations of the Respiratory Subcommittee related to a funding application from GlaxoSmithKline NZ Ltd for mepolizumab for the treatment of severe refractory eosinophilic asthma.

Recommendations

- 11.2. The Committee **recommended** mepolizumab be funded for patients with severe refractory eosinophilic asthma, using the Special Authority criteria as recommended by the Respiratory Subcommittee, with a **high priority**.

Discussion

- 11.3. The Committee noted the funding application for mepolizumab for the treatment of severe refractory eosinophilic asthma, relevant trials related to this application, relevant minutes and recommendations of the August 2017 Respiratory Subcommittee, as well as correspondence received from the supplier.
- 11.4. The Committee noted that mepolizumab targets human IL-5, the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab selectively and effectively inhibits eosinophilic airway inflammation by inhibiting IL-5 signalling and reducing the production and survival of eosinophils. The Committee noted that mepolizumab is formulated as a sterile lyophilised powder for injection, and is reconstituted with water for injection to 100 mg/mL prior to use. The Committee noted that mepolizumab is administered as a subcutaneous injection every 4 weekly.
- 11.5. The Committee noted Jia et al (J Allergy Clin Immunol 2013;131:695-703), a study which reviewed the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT). The Committee considered that the ACT was preferred over the ACQ, as it had good diagnostic accuracy for the assessment of controlled and poorly controlled asthma, and it was easily accessible to patients and clinicians in New Zealand.
- 11.6. The Committee noted Farne et al (Cochrane Database of Systematic Reviews 2017, CD010834), a Cochrane review conducted on several anti-IL-5 agents, including mepolizumab, which compared its effect on asthma exacerbations, health related quality of life (HRrQoL), and lung function relative to placebo. The Committee noted the review identified that treating with anti-IL-5 agents halved rates of clinically significant asthma exacerbations in patients with severe eosinophilic asthma compared to standard of care, but that despite there being modest improvements in HRQoL scores in patients treated with anti-IL-5, these reductions did not reach the minimum clinically important difference (MCID). All anti-IL-5 treatments produced a small but statistically significant improvement in the mean pre-bronchodilator FEV1.
- 11.7. The Committee noted Ortega et al (Lancet Respi Med 2016;4:549-56), a post-hoc analysis of pooled data from patients in the DREAM and MENSA studies, analysing the annual rate of clinically significant exacerbations stratified by baseline eosinophil counts. The Committee noted that the rates of exacerbations were related to the baseline eosinophil count. The relative rate (RR) for exacerbations was 0.48 (95% CI, 0.39 to 0.58) in patients with a baseline eosinophil count of at least 150 cells per μ L, and 0.30 (95% CI, 0.23 to 0.40) in patients with baseline count of at least 500 cells per μ L. The Committee therefore considered that the tight initiation criteria for mepolizumab, based on the criteria of having a high eosinophil count, would ensure that treatment would be targeted to those patients most likely to benefit.
- 11.8. The Committee considered mepolizumab to be the first registered treatment for severe eosinophilic asthma, and that it targets a disease with a high unmet health need which particularly affects Maori and Pacific populations. The Committee broadly agreed with the interpretation of the evidence as reviewed by the Respiratory Subcommittee in August 2017 and its recommendations. The Committee considered that there was good quality evidence demonstrating the benefit of mepolizumab, and that treating with mepolizumab is likely to result in reduced exacerbations, hospital

visits, and oral steroid use. The Committee recommended mepolizumab be funded for patients with severe refractory eosinophilic asthma, using the Special Authority criteria as recommended by the Respiratory Subcommittee, with a high priority
