

PTAC meeting held on 9 & 10 February 2017

(minutes for web publishing)

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016*.

Note that this document is not necessarily a complete record of the PTAC meeting; only the relevant portions of the minutes relating to PTAC discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

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1. Subcommittee Minutes

Haematology Subcommittee

- 1.1. The Committee noted and accepted the minutes of the Haematology Subcommittee teleconference held on 6 October 2016.

Diabetes Subcommittee

- 1.2. The Committee noted and accepted the minutes of the Diabetes Subcommittee meeting held 10 October 2016, with the following exceptions:

New Antidiabetic agents

- 1.3. Regarding paragraphs 6.1-6.18 (the Subcommittee's discussion on new antidiabetic agents), the Committee considered the Diabetes Subcommittee's recommendation that "in light of the new evidence, PTAC consider the three classes of antidiabetic agents separately rather than as a group, and consider applying separate Special Authority criteria to each one of the new classes of agents".
- 1.4. The Committee noted that it had previously reviewed all of the agents separately and that it had recommended funding for each agent with a low priority. Members noted that all new antidiabetic agents had been recommended for funding with a low priority, primarily due to their benefit with respect to affecting HbA1c to be considered comparable. The Committee noted that, based on the available evidence, it had previously considered that there was a lack of evidence supporting clinically significant benefits other than decreased HbA1c.
- 1.5. The Committee considered that, in the absence of more specific advice from the Subcommittee and in light of the new evidence regarding the antidiabetic agents, in particular, empagliflozin and liraglutide studies from the SGLT-2 inhibitor and GLP-1s groups, it would re-review these individual agents. The Committee noted that the Subcommittee considered that these agents could potentially have additional renal and cardiovascular health benefits.
- 1.6. The Committee considered that in the absence of studies that reported a class effect, it would consider empagliflozin and liraglutide separately, rather than the therapeutic class of agents. The Committee considered that the Subcommittee had noted that the studies demonstrating benefit were specifically on these agents and considered that the literature did appear to reflect that there was a class effect. However, the Committee considered that as part of a review of these chemicals, the class effect is likely to require consideration at the same time. The Committee considered that it would consider these agents with respect to and in the context of the current international guidelines for use of these agents.
- 1.7. The Committee noted that it had previously reviewed evidence of the benefits of these agents compared with placebo, and considered this to be less useful than reviewing studies comparing the benefit of these agents with insulin. Members considered that studies of the agents versus insulin would be most clinically relevant, and in the absence of any direct comparisons, indirect comparisons regarding delay to commencement on insulin would be of value for its re-review of these particular agents (empagliflozin and liraglutide).

Ketone testing

- 1.8. Regarding paragraph 4.8 (the Subcommittee's discussion on urine ketone test strips) Members considered that although people with Type 1 diabetes in Australia use blood ketone testing, and have access to both blood and urine ketone testing, these pharmaceuticals are not funded under the PBS and patients in Australia privately purchase these products.

Anti-infective Subcommittee

- 1.9. The Committee noted the minutes of the Anti-infective Subcommittee of PTAC meeting held on 13 October 2016 and accepted recommendations relating to 4.18, 4.24, 4.32, 4.37, 4.38, 4.50, 5.2, 5.3, 8.10, 8.11 and 8.12.
- 1.10. The Committee noted the Anti-infective Subcommittee's comments regarding use of nitrofurantoin in the elderly. The Committee raised concerns regarding the evidence base supporting use of nitrofurantoin in the elderly and those with renal impairment. The Committee noted the request of the Subcommittee in paragraph 4.5 and recommended that PHARMAC staff provide more detail on the use of trimethoprim and nitrofurantoin in both prescribed and over-the counter prescribing (pharmacist prescribed) for review at the next Anti-infective Subcommittee meeting.
- 1.11. The Committee noted that the Anti-infective Subcommittee supported PTAC's recommendation in paragraph 4.11 to reduce the tube size of fusidic acid 2% cream and ointment and mupirocin 2% ointment to a single-use 5 g tube for dermatological applications.
- 1.12. The Committee supported the Anti-infective Subcommittee's recommendation to seek a larger 2% hydrogen peroxide tube (50 g) and promote its use over other topical antibiotics. In regard to paragraphs 4.11 and 6.6, Members noted the high use of these antibiotics by nurse practitioners and recommended ongoing education to nurse practitioners on anti-microbial stewardship and appropriate prescribing.
- 1.13. The Committee supported the recommendations of the Anti-infective Subcommittee in item 6, but raised the concern that it may be difficult to restrict the use of azithromycin due to its relative efficacy as well as the ability of patients to purchase azithromycin without subsidy themselves via a prescription where they do not meet the endorsement criteria.
- 1.14. The Committee noted the recommendation of the Anti-infective Subcommittee in paragraph 7.1 that the proposal for funding levofloxacin for second line *H. pylori* eradication be declined and requested further feedback from the Gastrointestinal Subcommittee.

Immunisation Subcommittee

- 1.15. The Committee noted and accepted the minutes of the Immunisation Subcommittee of PTAC meeting held on 18 November 2016 and accepted recommendations related to paragraphs 7.9, 8.9, 8.10, 8.13, 8.14, 10.6, and 10.10.
- 1.16. The Committee noted that a number of recommendations from the Subcommittee related to recommendations to PHARMAC staff (paragraphs 7.9, 8.5, 10.2, 10.7, and 10.10).
- 1.17. The Committee noted the Immunisation Subcommittee's recommendation in paragraph 8.8 to the Ministry of Health to extend the funding of the influenza vaccination programme to 31 December each year.
- 1.18. The Committee noted the recommendation by the Subcommittee in paragraph 10.5 and recommended that PHARMAC request that the Immunisation Advisory Centre (IMAC) present a formal application to PHARMAC to increase the number of funded haemophilus influenza type B vaccines from one to three for consideration by the Immunisation Subcommittee.
- 1.19. In regards to paragraph 10.7, the Committee agreed with the Immunisation Subcommittee that the specific needs of patients at various stages of kidney disease needed to be better defined and that PHARMAC should seek further advice from the Nephrology Subcommittee. The Committee also requested that PHARMAC provide information detailing the current use of vaccines in patients with renal failure. The Committee noted this issue was referred to the Nephrology Subcommittee at its December 2016 meeting.

and that minutes from that discussion will be provided to PTAC in May 2017.

- 1.20. The Committee noted that paragraph 10.2 included several action points for PHARMAC staff to request funding applications from relevant clinicians for widened access to Tdap vaccine for patients living with HIV, for meningococcal vaccine booster for patients with long term immunosuppression, and influenza vaccine for patients with chronic liver disease.

Neurological Subcommittee

- 1.21. The Committee noted and accepted the minutes of the Neurological Subcommittee meeting held on 7 November 2016, with the following exceptions.
- 1.22. Regarding paragraphs 6.11-6.21 (the Subcommittee's review of PTAC's August 2016 reviews of deflazacort for Duchenne Muscular Dystrophy, and rituximab for myasthenia gravis), the Committee noted that this would be discussed separately at the meeting under Matters Arising.
- 1.23. Regarding paragraphs 6.30-6.39 (the Subcommittee's review of midazolam ampoules being available on a Practitioner's Supply Order (PSO) for the treatment of status epilepticus), the Committee agreed with the recommendation that two ampoules of midazolam (5 mg per ml, 3 ml plastic ampoules) for the treatment of status epilepticus be available on a PSO with a high priority. However, the Committee considered there could be a risk of use for other indications unless access was restricted to status epilepticus. The Committee considered that there may be a desire to use midazolam ampoules, if available on a PSO, for mental health crisis in remote/rural settings and for conscious sedation, and that these indications would need separate consideration prior to widening access via a PSO.
- 1.24. Regarding paragraphs 6.42-6.47 (the Subcommittee's discussion of a potential commercial process for gabapentin and pregabalin), the Committee considered that the Analgesic Subcommittee should be involved in reviewing estimated patient numbers. The Committee noted that although gabapentin is listed in the Neurology therapeutic group, pain medicine specialists are also involved with managing patients with acute and chronic neuropathic pain. The Committee also noted evidence had been published regarding reporting bias with some of the published gabapentin studies and considered that in light of this, the Analgesic Subcommittee should re-review the evidence for gabapentinoids at its next Subcommittee meeting.

Mental Health Subcommittee

- 1.25. The Committee noted and accepted the minutes of the Mental Health Subcommittee meeting held on 23 November 2016, with the exception of item 6 (the Subcommittee's review of a funding application for paliperidone 3-monthly depot injection [Invega Trinza]) which was scheduled to be reviewed by the Committee later in the meeting.
- 1.26. The Committee noted the high proportion of oral antipsychotic expenditure on aripiprazole tablets relative to its proportion of oral antipsychotic prescribing. The Committee suggested that PHARMAC explore the possibility of developing stricter renewal criteria for aripiprazole (e.g. with measures of clinical benefit) as a means to ensure that only patients gaining significant benefit from treatment have ongoing funded access.
- 1.27. **[Withheld]**
- 1.28. The Committee noted the Subcommittee's support for the listing of zopiclone 3.75 mg tablets alongside the current listing of zopiclone 7.5 mg tablets (paragraphs 5.33-5.36). The Committee also supported the listing of zopiclone 3.75 mg tablets as a harm reduction mechanism to reduce the overall dose of zopiclone taken by patients. The Committee noted that there are other non-pharmacological approaches to the management of insomnia that would also be beneficial to promote more widely.

2. Matters Arising / Correspondence

Micronutrients for people with Attention Deficit Hyperactivity Disorder (ADHD)

- 2.1. The Committee noted correspondence from the applicant in relation to PTAC's comments in November 2016 regarding the Committee's willingness to reconsider the application should further robust placebo-controlled trial publications become available that were sufficiently powered over a suitable timeframe with a well-described product.
- 2.2. The Committee clarified that it wished to see publications of studies that were adequately powered to detect clinically relevant outcomes to the child and family, and not surrogate or poorly defined outcomes. The Committee noted that, ideally, the studies should contain the same product (i.e. with the same component composition and quantities) as the product that was the subject of the funding application.

Deflazacort

- 2.3. The Committee noted that in November 2016 the Neurological Subcommittee reviewed the minutes of PTAC's August 2016 review of deflazacort for Duchenne Muscular Dystrophy (DMD) for patients unable to tolerate prednisone. The Committee noted that the Subcommittee had considered that, in light of a recently published randomised controlled trial, PTAC should review its recommendations.
- 2.4. The Committee appreciated the evidence that the Subcommittee provided and noted that Griggs et al. (Neurology 2016; DOI 10.1212/WNL.0000000000003217) was a double blind, placebo controlled randomised controlled trial assessing safety and efficacy of deflazacort and prednisone versus placebo among 196 boys with DMD during a 52-week period. The Committee noted the primary endpoint was the change from baseline to week 12 in average muscle strength and that secondary endpoints included changes in average muscle strength from week 12 to week 52 and in pulmonary functional testing. The Committee noted that after 12 weeks of treatment both deflazacort and prednisone reportedly improved muscle strength compared with placebo. The Committee noted that in secondary analysis of change in muscle strength from 12 to 52 weeks there was a significant improvement in average muscle strength score from in the deflazacort 0.9 mg/kg/d group compared with the prednisone treated group; however, the difference for the deflazacort 1.2mg/kg/d compared with prednisone did not reach statistical significance. The Committee noted that deflazacort was associated with less weight gain than prednisone, and noted that this difference was approximately 2kg over a 1-year period. The Committee considered that a difference in weight gain of ~2kg over a year was likely to be clinically meaningful; however, with regards to DMD, outcomes relating to disease specific metrics such as ambulation would be more clinically relevant.
- 2.5. The Committee noted the time period that had elapsed from completion of the study (1995) to publication (2016) and the large number of tests for statistical significance for multiple outcomes that were not predefined as primary or secondary endpoints. The Committee considered the publication did not provide strong evidence of clinically relevant differences between the two treatments. The Committee noted that the publication did not provide any evidence regarding statistically significant differences in behavioural side effects between the two treatments; being one of the key outcomes of interest in the funding application.
- 2.6. At its previous consideration, the Committee noted that the available evidence did not support a benefit of deflazacort over prednisone in the requested patient population; and that this included consideration of a Cochrane review of the use of corticosteroids in DMD (Matthews et al. Cochrane Database Syst Rev. 2016;5:CD003725). The Committee noted that the 2016 Cochrane review did not include the Griggs et al. publication; however, the review reported 3 RCTs with data up until year 2015 comparing deflazacort with prednisone. The Committee considered that the Griggs et al. (2016) trial results did not differ in effect from the relevant results in the Cochrane review, and the Committee's view remained unchanged; however, the Committee reiterated that it would like to review its

recommendation once the FOR-DMD study (Clinical Trials.gov Identifier: NCT01603407) was published.

- 2.7. The Committee again recommended that the application for the funding of deflazacort for the treatment of patients with DMD who are unable to tolerate prednisone be declined.

Rituximab for myasthenia gravis

- 2.8. The Committee noted that in November 2016 the Neurological Subcommittee reviewed the minutes of PTAC's August 2016 review of rituximab for myasthenia gravis.
- 2.9. The Committee appreciated the Subcommittee's feedback and noted the Subcommittee's advice that rituximab would not be used in an acute setting to control an exacerbation. The Committee noted that, given this information, its previous recommendation for widening access to patients with severe, rapidly progressive myasthenia gravis, as a third line treatment, with a high priority (12.2 of the August 2016 minutes) would therefore not likely be a priority for funding as this is not the setting that it would be used in.
- 2.10. The Committee noted that the Neurological Subcommittee defined the patient population that it considered should be treated with rituximab as the 'severe refractory group', the group for which PTAC had recommended funding with a low priority (12.3 of the PTAC August 2016 minutes). The Committee agreed with the restrictions, as proposed by the Neurological Subcommittee, for this group.
- 2.11. The Committee noted that it had previously considered that the available studies for rituximab in MG consisted of case reports and small uncontrolled observational cohort studies. The Committee considered that given there has been no new robust evidence provided, its **recommendation** for funding for this 'severe refractory group' (12.3 of the PTAC August 2016 minutes) remains with a low priority.

Haemophilia Treatments

- 2.12. The Committee noted correspondence from the Haemophilia Treaters Group (HTG) in relation to Recombinant Factor VIII and IX Fc Fusion Proteins - Haemophilia A & B considered by PTAC at its August 2016 meeting.
- 2.13. The Committee noted the HTG's view that all patients, apart from those previously untreated, would likely change to the longer acting products if available.
- 2.14. The Committee considered there was potential for a substantial increase in already high expenditure associated with haemophilia treatment if the longer acting products came at a higher overall cost. Given the lack evidence of improved clinical outcomes, the Committee considered its previous 'only if cost-neutral to the short-acting products' recommendations remained appropriate.

[Withheld]

Ibrutinib for the treatment of 17p deletion or TP53 mutation chronic lymphocytic leukaemia (CLL)

- 2.15. The Committee noted that an application for funding of ibrutinib (Imbruvica, Janssen) for the treatment of patients with high risk CLL and mantle cell lymphoma had been considered by PTAC and CaTSOP on a number of previous occasions. The Committee noted that there were current recommendations regarding funding for all patient groups applied for except patients with 17p or TP53 CLL. The Committee noted that at its meeting in November 2016 PTAC had deferred making a recommendation regarding ibrutinib for 17p CLL pending its review of the published results of the RESONATE 17 study.
- 2.16. The Committee noted that RESONATE-17 was a phase 2, open label, single arm, study of ibrutinib (420 mg daily until progression) in 144 patients with symptomatic relapsed or refractory previously treated 17p deletion CLL (n=137) or small lymphocytic leukaemia

(n=7).

- 2.17. The Committee noted unpublished results from RESONATE-17 (O'Brien et al. ASH 2014 abstract) had been considered at previous meetings and that updated results had recently been published as O'Brien et al. *Lancet Oncol* 2016;17:1409-18.
- 2.18. The Committee noted that in the post-hoc investigator-assessed extended analysis, at a median follow-up of 27.6 months (IQR 14.6–27.7), overall response was reported in 120 (83%) of patients (95% CI 76–89; 92 [64%] had a partial response, ten [7%] had a partial response with lymphocytosis, three [2%] had a nodular partial response, 12 [8%] had complete response, and three [2%] had complete response with incomplete bone marrow recovery), with 72 (50%) of 144 patients continuing on ibrutinib treatment.
- 2.19. The Committee noted that in the extended analysis, median PFS was not reached (95% CI 27.7 to not estimated), with an estimated progression-free survival at 24 months of 63% (95% CI 54–70). The Committee noted that median overall survival was not reached (95% CI 29.5 to not estimated), and the estimated 24-month overall survival was 75% (95% CI 67–81).
- 2.20. The Committee considered that the published data was promising and appeared to be robust although, as this was a single-arm non-randomized or controlled study, there was a level of uncertainty regarding the magnitude of benefit of ibrutinib in this population. The Committee considered the current price being proposed was adversely affecting the cost-effectiveness of ibrutinib.
- 2.21. The Committee considered that CLL patients with 17p deletion mutations have fewer currently funded treatment options and generally have a worse prognosis and poorer response to therapy compared with CLL patients without these genetic mutations.
- 2.22. The Committee recommended that ibrutinib for the treatment of CLL with chromosome 17p deletion or TP53 mutation CLL at diagnosis or relapse be funded with medium priority, subject to the Special Authority recommended by the Cancer Treatments Subcommittee at its meeting in September 2016, noting the high health need in this population.
- 2.23. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Pertuzumab for patients with previously treated HER-2 positive metastatic breast cancer

- 2.24. The Committee noted correspondence from the New Zealand Breast Cancer Foundation and Breast Cancer Aotearoa Coalition regarding the recent decision to fund pertuzumab (Perjeta, Roche) for patients with treatment naïve HER2 positive metastatic breast cancer and requesting consideration of extending funded access to pertuzumab for all patients currently being treated with trastuzumab for metastatic breast cancer.
- 2.25. The Committee noted that pertuzumab is registered in New Zealand for use 'in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease'. The Committee noted that use of pertuzumab in non-treatment naïve settings would be for an unapproved indication.
- 2.26. The Committee noted that pertuzumab was listed on the Pharmaceutical Schedule from 1 January 2017 for the treatment of patients with HER2 positive metastatic breast cancer who have not received prior treatment for their metastatic disease subject to Special Authority criteria based on the eligibility criteria for the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study (Baselga et al. *NEJM*. 2012;366:109-19; Swain et al. *Lancet Oncology* 2013;14:461-71).

- 2.27. The Committee noted the key evidence to support the use of pertuzumab for patients currently receiving trastuzumab treatment for their metastatic disease is based on 48 women without disease progression in the control arm (trastuzumab/docetaxel and placebo, n=406) of the CLEOPATRA study (Swain et al. NEJM 2015;372:724-34) who after 2 years or more of treatment crossed over to receive pertuzumab in combination with trastuzumab and docetaxel. Crossover patients were excluded from reported survival data at the time of their first pertuzumab dose.
- 2.28. The Committee noted that an overview of the CLEOPATRA study (Herold et al. J Adv Pract Oncol 2016;7:839) reports that in the 48 crossover patients, the median progression free survival improved by 6.3 months and the median duration of response improved by 7.7 months. The Committee considered that the source of this data was unclear. The Committee noted that PHARMAC staff had been informed by the supplier of pertuzumab that they had been in recent contact with the principal author of the CLEOPATRA study, Prof Sandra Swain, who advised that she is not aware of further data to support this treatment option.
- 2.29. The Committee considered that, based on the currently available published evidence, it was not possible to determine the level of benefit trastuzumab pre-treated patients may achieve from the addition of pertuzumab or whether response differed depending on duration of prior trastuzumab treatment.
- 2.30. The Committee noted that data for the use of pertuzumab in a second-line setting from the PHEREXA trial were presented at the 2016 ASCO meeting. The Committee noted PHEREXA was a phase III study of trastuzumab + capecitabine with (n=228) or without (n=224) pertuzumab for patients who received a prior taxane and progressed during/after one line of trastuzumab-based therapy in the HER2-positive metastatic breast cancer setting.
- 2.31. The Committee noted data for the use of pertuzumab combined with trastuzumab in 66 patients with HER2 positive advanced breast cancer who had experienced disease progression during prior trastuzumab based therapy from a phase II, open-label, single-arm, exploratory study with a Simon two-stage design (Baselga et al. JCO 2010;28:1138-44).
- 2.32. The Committee considered that currently available evidence was of moderate strength and poor quality but as there was a significant cohort of trastuzumab pre-treated HER2 metastatic breast cancer patients globally further data would likely emerge to support the use of pertuzumab for patients who have had previous treatment with trastuzumab for their metastatic HER2 positive breast cancer.
- 2.33. The Committee deferred making a recommendation regarding the funding of pertuzumab for previously trastuzumab treated HER-2 positive metastatic breast cancer pending publication of further evidence to support its use in these settings.
- 2.34. The Committee considered that published evidence for the use of pertuzumab in non-treatment naïve metastatic breast cancer settings should be referred to CaTSOP once available and noted it would be beneficial if both survival and quality of life data were provided.

Tiotropium Bromide

- 2.35. The Committee noted and reviewed correspondence received from Boehringer Ingelheim dated 16 January 2017 requesting PHARMAC withhold publication of the minutes of the Pharmacology and Therapeutics Advisory Committee (PTAC) 3-4 November 2016 meeting regarding tiotropium bromide for treatment of severe asthma.
- 2.36. The Committee noted that Boehringer Ingelheim, in its correspondence, requested that the entire section of the minutes relating to tiotropium bromide for severe asthma be withheld from publication on grounds that:

- There are "...a number of significant inaccuracies stated in the minutes resulting in interpretation of the clinical data in asthma which is not consistent with assessments made by international regulatory bodies as well as established respiratory experts in the field."
- "In particular, the minutes have raised concerns about the safety of tiotropium Respimat based on 3 systematic reviews and meta-analyses. Since publication of these analyses, the safety of tiotropium Respimat in COPD has been thoroughly investigated and confirmed by the TIOSPIR study. Therefore, we have concerns regarding speculation and assumptions made about the safety in asthma, based on superseded meta-analyses in COPD".
- That Boehringer Ingelheim "has serious concerns that the current content of the minutes (if made public) could prejudice the health and safety of patients currently on treatment with tiotropium Respimat in COPD and would also likely unreasonably prejudice the commercial position of tiotropium Respimat in both COPD and asthma in and outside of NZ. Statements made in the minutes based on historical and superseded data have the potential to cause significant and unnecessary concern among many patients already prescribed tiotropium Respimat for the treatment of COPD, in accordance with the Special Authority approved by PHARMAC. The potential for patients to unnecessarily stop medication will lead to significant health risks for NZ patients."

2.37. The Committee noted that Boehringer Ingelheim referred to the TIOSPIR study (Wise et al., N Engl J Med 2013;369:1491-501) as additional supporting evidence for the safety of tiotropium, however the Committee noted that the TIOSPIR study was part of Boehringer's original submission, which has already been reviewed and considered by PTAC at its November 2016 meeting.

2.38. The Committee noted that in its correspondence, Boehringer Ingelheim had provided an editorial (Jenkins, N Engl J Med. 2013;369:1555-6) as additional evidence to support its view regarding the concerns noted above. The Committee considered that this editorial did not change its previous view, as minuted at its November 2016 meeting.

2.39. Members also noted an editorial by Beasley and Jenkins (Jenkins et al., Thorax, 2013;68:5-6) and considered that prominent respiratory researchers had expressed safety concerns regarding tiotropium bromide Respimat.

2.40. The Committee considered that the recommendation to decline the submission for tiotropium bromide for the treatment of severe asthma was based more on uncertainty around the clinical benefit of tiotropium bromide when used in patients with severe asthma, rather than specifically related to the safety of tiotropium bromide.

2.41. The Committee considered that the minutes of the Pharmacology and Therapeutics Advisory Committee (PTAC) November 2016 meeting regarding tiotropium bromide for treatment of severe asthma adequately reflected the discussion, and in the absence of new evidence (other than the Jenkins editorial), considered that no amendments or redactions to this minute were necessary.

2.42. The Committee also noted that the TIOSPIR study (Wise et al., NEJM 2013) was incorrectly referenced in paragraph 15.5 of the November 2016 minutes. The Committee considered that the minute should be corrected to address this (additions in bold, deletions in strikethrough):

"The Committee considered that there is uncertain risk with the long term use of the Respimat device, especially since patients with cardiovascular co-morbidities were excluded from the 48 week trial. The Committee noted that 3 independent systematic reviews and meta-analyses (BMJ 2011, Cochrane Review 2012) and Thorax 2012) of randomised placebo controlled trials of tiotropium Respimat, each using different methods, have demonstrated a 50% increased risk of mortality with its use in patients with COPD. The Committee noted the Wise et al. study (NEJM 2014 **2013**), a supplier

funded randomised, double-blind parallel-group trial involving 17,135 patients with COPD comparing the safety of the Respimat at a once daily dose of 2.5 mcg or 5 mcg with tiotropium HandiHaler at a once daily dose of 18 mcg. In this study, Respimat was reported to be noninferior to HandiHaler for death from any cause (Respimat at a dose of 5 mcg versus HandiHaler at a dose of 18 mcg ([HR] 0.96; 95% CI, 0.84 to 1.09). The Committee considered it would be difficult to draw firm conclusions on mortality risk in asthma trials given the low mortality rates compared with COPD.”

3. Widening of access of IV Epoprostenol for Functional Class III -IV Pulmonary Arterial Hypertension

Application

- 3.1. The Committee considered an application from a clinician, on behalf of a group of respiratory and cardiovascular clinicians, for the listing of epoprostenol in the community Pharmaceutical Schedule for:
1. Patients presenting acutely with idiopathic pulmonary arterial hypertension (iPAH) in New York Heart Association/World Health Organization (NYHA/WHO) Functional Class IV.
 2. Patients deteriorating rapidly to NYHA/WHO Functional Class IV who may be lung transplant recipients in the future, if their disease is stabilised.
 3. Patients with PAH associated with the scleroderma spectrum of diseases (APAH-SSD) who have no major comorbidities and are declining on combination therapy.

Recommendation

- 3.2. The Committee **recommended** that the application for epoprostenol listing in the community Pharmaceutical Schedule be listed with a medium priority for each of these indications:
1. Patients presenting acutely with idiopathic pulmonary arterial hypertension (IPAH) in New York Heart Association/World Health Organization (NYHA/WHO) Functional Class IV
 2. Patients deteriorating rapidly to NYHA/WHO Functional Class IV who may be lung transplant recipients in the future, if their disease is stabilised
 3. Patients with PAH associated with the scleroderma spectrum of diseases (APAH-SSD) who have no major comorbidities and are declining on combination therapy
- 3.3. The Committee **recommended** that advice should be sought from the Cardiovascular and/or Respiratory Subcommittees and/or the PHARMAC PAH Panel regarding a suitable framework for treatment of patients with PAH and consideration of the place of epoprostenol in therapy, noting PTAC's recommendations regarding widening of access of these treatments. The Committee considered that this proposed framework should then be brought back to PTAC for review.
- 3.4. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 3.5. The Committee noted its previous recommendations and the minutes from these discussions for treatment of Pulmonary Arterial Hypertension, including:
1. Widening of access to PAH treatments (May 2016 PTAC meeting, November 2016 PTAC meeting) for,
 - a. Patients in FCII that do not have clear evidence of disease progression, recommended funding with a low priority
 - b. Dual therapy, recommended funding with a high priority
 - c. Triple therapy, recommended funding be declined, except for patients who are on the active lung transplant list and for this group, recommended funding with a high priority.

- d. Goal directed therapy, where it considered that there was little evidence available and no recommendation was given.
 2. Selexipag (May 2016 PTAC meeting), recommended funding with a low priority
 3. Macitentan (May 2015 PTAC meeting), recommended funding with a low priority
 4. Epoprostenol for patients with PAH on the active lung transplant list (November 2014 PTAC meeting) recommended funding with a high priority
- 3.6. For clarity, the Committee considered at its previous meetings that widening of access to PAH treatments (number 1, above) would apply to the following groups of patients who are eligible for PAH treatment using the PHARMAC 2009 eligibility criteria:
1. Dual therapy in the community using the currently funded agents, in patients that are currently eligible for funded treatment, was recommended with a high priority. Dual therapy may be sildenafil with bosentan, sildenafil with ambrisentan, sildenafil with iloprost, ambrisentan with iloprost, bosentan with iloprost.
 2. Triple therapy in the community using the currently funded agents for patients on the active lung transplant list, was recommended with a high priority. Triple therapy would consist of sildenafil, bosentan or ambrisentan, and nebulised iloprost.
 3. Triple therapy in the community using the currently funded agents for patients who are not on the active lung transplant list was declined.
 4. Patients with NYHA/WHO FCII disease at the time of diagnosis (i.e. without clear evidence of disease progression) being able to access currently funded treatments as per the more severe patients (i.e. NYHA/WHO FCII patients who are deteriorating rapidly)
- 3.7. The Committee noted that at the time of making these recommendations, epoprostenol was not funded in the community, so these recommendations exclude treatment with epoprostenol.
- 3.8. For consistency with the above recommendations and according to the clinician submission, the Committee considered that this application for epoprostenol was effectively for:
1. Dual therapy for the following patients:
 - a. Patients presenting acutely with idiopathic pulmonary arterial hypertension (IPAH) in New York Heart Association/World Health Organization (NYHA/WHO) Functional Class IV
 - b. Patients deteriorating rapidly to NYHA/WHO Functional Class IV who may be lung transplant recipients in the future, if their disease is stabilised
 - c. Patients with PAH associated with the scleroderma spectrum of diseases (APAH-SSD) who have no major comorbidities and are declining on combination therapy
 2. Triple therapy for patients who are on the active lung transplant list,
- 3.9. The Committee noted that at its November 2014 meeting, it recommended that epoprostenol for patients with PAH who are on the active lung transplant list, be listed in Section H of the Pharmaceutical Schedule with a high priority, and that since 1 September 2015, IV epoprostenol has been on the Hospital Medicines List (HML) with a restriction for patients with PAH who are on the active lung transplant list.
- 3.10. The Committee noted that sildenafil, bosentan, ambrisentan and nebulised iloprost are currently listed in the community Pharmaceutical Schedule, and that intravenous and nebulised iloprost and epoprostenol are listed in the HML. The Committee noted that epoprostenol is currently listed with a restriction (noted above) and that intravenous iloprost is listed without any restrictions.
- 3.11. The Committee noted that PAH treatments are currently funded according to the 2009 eligibility criteria for the treatment of PAH, and that access to these treatments is administered by the PHARMAC Pulmonary Arterial Hypertension Panel. The Committee noted that the group of clinicians that supported this application included members of the

PHARMAC PAH Panel.

- 3.12. The Committee noted its recommendation from the November 2016 PTAC meeting, that “triple therapy in patients with PAH be declined, except in the situation where patients were on an active transplant list”, which was recommended with a high priority. The Committee noted that the applicant indicated that use of epoprostenol, if funded in the community setting, would replace endothelin receptor antagonists (bosentan and ambrisentan) and nebulised iloprost. The Committee noted that the applicant considered that if access to epoprostenol in the community was available for the indications above, these patients would be treated with epoprostenol in combination with sildenafil.
- 3.13. Members considered that if epoprostenol was listed for the indications requested by this application, this could potentially lead to triple therapy being used in practice. Members considered that if epoprostenol was listed for these indications that patients with PAH could be on epoprostenol, sildenafil, and an endothelin receptor agonist, unless restricted accordingly (noting PTAC’s recommendation to decline the use of triple therapy in PAH).
- 3.14. The Committee noted the evidence supplied by the applicant and additional articles, including:
- Barst et al., (N Engl J Med 1996; 334:296-301)
 - Reichenberger et al., (Pulmonary Pharmacology & Therapeutics 2011 24:169-73)
 - Sitbon et al. (J Am Coll Cardiol 2002; 40:780-8)
 - European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PAH (Eur Heart J. 2016 ;37:67-119)
 - Rubenfire et al. (Chest. 2013;144:1282-90)
 - Shirai et al. (Mod Rheumatol. 2013; 23:1211-20)
 - Sitbon et al. (Eur Respir J 2014;43:1691-7)
 - Taichman et al. (Chest. 2014;146:449-75)
 - Launay et al. Annals of the Rheumatic Diseases 2013;72:1940-6).
- 3.15. The Committee noted Barst et al., (N Engl J Med 1996;334:296-301) a 12 week prospective, randomised, multicentre, non-blinded trial to study the effects of continuous IV epoprostenol infusion plus conventional therapy versus conventional therapy in 81 patients with severe primary pulmonary hypertension (NYHA FC III or IV). The authors reported an increase in 6 minute walk distance in patients treated with epoprostenol (from 315m at baseline to 362m at 12 weeks). Haemodynamic measurements also improved at 12 weeks in the epoprostenol group. Patients treated with IV epoprostenol reported frequent minor complications such as jaw pain, diarrhoea, flushing, headaches, nausea and vomiting. Serious complications were a result of the delivery system and included 4 episodes of non-fatal catheter-related sepsis and one non-fatal thrombotic event. Additional problems related to the delivery system included irritation or infection at the catheter site in 7 patients, bleeding at the catheter site in 4 patients, and catheter site pain in 4 patients. The Committee considered that a limitation of the study was that the trial did not report which vasodilators the participants received and considered that the comparator may not be the current standard of care for New Zealand patients. The Committee noted that the duration of this study was 12 weeks, and considered that longer term outcomes were uncertain.
- 3.16. The Committee noted Reichenberger et al, (Pulmonary Pharmacology & Therapeutics 2011;24:169-73) a comparison of intravenous epoprostenol versus high-dose inhaled iloprost in 24 participants. The authors reported that participants treated with intravenous epoprostenol had a longer ‘event-free’ period compared to inhaled high-dose iloprost (21 months for IV epoprostenol versus 16 months for inhaled high-dose iloprost, p = 0.049). The Committee considered that the definition of ‘event’ was unclear, as it had not been explicitly stated in the paper.
- 3.17. The Committee noted Sitbon et al. (J Am Coll Cardiol 2002; 40:780-8) a retrospective

study of 178 patients with primary pulmonary hypertension NYHA WHO functional class III or IV, who were on maximal oral therapy to determine the factors associated with long-term survival in patients with primary pulmonary hypertension treated with continuous epoprostenol infusion. The authors reported overall survival rates at one, two, three and five years as 85%, 70%, 63% and 55% respectively (compared with 58%, 43% 33% and 28% in the historical control group, $p < 0.0001$) and concluded that survival in patients treated with epoprostenol depends on the severity at baseline, as well as the 3-month response to therapy. The authors reported frequent minor complications of jaw pain, headache, diarrhoea, flushing, leg pain, nausea and vomiting, and 76 episodes of catheter-related sepsis in 53 patients (0.19 infections per patient-year). The Committee considered that the survival curves reported in this study were not necessarily evidence of increased survival despite improvements in their functional class (move from NYHA/FC III to FCII, for example).

- 3.18. The Committee noted Badesch et al. (Ann Intern Med 2000;132:425-34), an open-labelled, randomised controlled trial on the use of continuous IV epoprostenol in 111 patients with moderate to severe pulmonary hypertension due to scleroderma were measured over a 12 week period. The authors reported improved exercise capacity with a between treatment difference in median 6MWD of 108m (95% CI, 55.2-180m; $P < 0.001$) and improved haemodynamic parameters, with reductions in mean pulmonary artery pressure and pulmonary vascular resistance in the epoprostenol group after 12 weeks of treatment, however the Committee questioned the clinical significance of these differences as pulmonary artery pressures remained well above the upper limits of normal. The authors reported that 21 patients in epoprostenol group had improved WHO/NYHA functional class and no patients in the conventional therapy group. Improved dyspnoea and fatigue scores were also reported in the epoprostenol group. No difference in mortality was reported. The Committee considered that these functional differences were clinically significant.
- 3.19. The Committee noted the European Society of Cardiology/European Respiratory Society Guidelines and noted that they recommend that the same treatment algorithm is used for patients with SSc and IPAH patients.
- 3.20. Based on the available studies, the Committee considered that limitations of the published evidence were that there were no New Zealand participants in the studies, and considered that all were small un-blinded trials of low quality and poor strength.
- 3.21. The Committee noted that there were no published randomised controlled trials comparing the efficacy of loprost and epoprostenol in patients with PAH, and Members considered that epoprostenol, rather than iloprost, was used more widely for this indication internationally.
- 3.22. Members considered that treatment with epoprostenol in the community would be likely to be used as a chronic treatment as opposed to an acute one, and that the alternatives were lung transplantation or death. However, members also considered that there was no new evidence regarding the use of epoprostenol in PAH and that the available evidence did not report that epoprostenol extended survival in the patient groups considered in the application.
- 3.23. The Committee considered that the health need of people with PAH is high, particularly in patients with NYHA/WHO Functional class IV disease. The Committee considered that patients with IPAH-SSD with no major comorbidities could be considered as having the same health need as patients with PAH due to other causes, as the NYHA/WHO Functional Class classification underlies both groups.
- 3.24. The Committee noted that inhaled iloprost is prescribed and administered four times a day and that pharmacologically it has a short half-life. Members considered that this intermittent form of administration limits its practicality and therefore its use in practice.

- 3.25. The Committee noted that epoprostenol is a prostacyclin analogue, administered intravenously through a central vein, and is a potent arterial vasodilator and platelet aggregator, with a half-life of 2-6 minutes. Members considered that as epoprostenol is a non-selective pulmonary vasodilator it may worsen ventilation-perfusion (VQ) mismatch and cause hypotension, which is a disadvantage. However, Members also considered that the intravenous route allowed better titration of effect than the inhaled route. The Committee considered that due to its potency, administration of the correct dose of epoprostenol was important in order to avoid severe hypotension requiring inotropic support. The Committee noted that other adverse effects of epoprostenol included headache, jaw pain, flushing, nausea, diarrhoea, skin rash, and musculoskeletal pain.
- 3.26. The Committee noted that the maximum infusion rate indicated in the applicant submission was 15ng/kg/min, compared to the higher infusion rates observed in some study participants in the studies. Given this, the Committee considered that should epoprostenol be listed on the community Pharmaceutical Schedule, the average daily dose used in practice may be higher than the applicant's estimate.
- 3.27. The Committee considered that the applicant's estimate of 8-10 people who would receive epoprostenol in the community was realistic, however members also considered that patient numbers were likely to increase over time due to a potential symptomatic benefit in all patients with iPAH.
- 3.28. The Committee considered that the cost of potential complications of epoprostenol therapy should be taken into account, particularly the costs for treating a central venous line infection. The Committee considered that insertion of a long-term central venous line, treatment of central venous line infection and sepsis, provision of a community nurse to monitor therapy, troubleshooting pump delivery malfunctions, and provision of education would be important to include in the cost utility analysis. The Committee considered that patients on epoprostenol in the community would also need to be highly motivated (e.g. for sterile reconstitution of epoprostenol and aseptic administration technique, and to monitor and carry a spare pump with them at all times) and would be required to have a refrigerator and mobile phone access. The Committee considered that the cost of the pump(s) and consumables would also need to be factored in should epoprostenol be listed on the community schedule.
- 3.29. The Committee considered that, in practice, clinicians would be expected to treat patients with either inhaled iloprost or intravenous epoprostenol (not both agents together) due to these agents being in the same pharmaceutical class (prostacyclin analogues).
- 3.30. The Committee considered that inhaled iloprost would be the appropriate comparator to epoprostenol for a community listing.

4. Sacubitril with valsartan for heart failure with reduced ejection fraction

Application

- 4.1. The Committee reviewed an application from Novartis New Zealand Ltd for the listing of sacubitril/valsartan (Entresto) for the treatment of heart failure in patients with New York Heart Association (NYHA) class II-IV heart failure and an ejection fraction of less than or equal to 40%.

Recommendation

- 4.2. The Committee **recommended** that sacubitril/valsartan be funded for the treatment of heart failure in patients, as per the proposed Special Authority criteria below (pending Cardiovascular Subcommittee review), with a low priority.

Initial application

Applications from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

- 1 Patients with NYHA classes III-IV; and
- 2 Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 35-40%; and
- 3 Patient must receive concomitant optimal standard chronic heart failure treatments

Renewal from any relevant practitioner. Approvals valid for 12 months for applications where the treatment remains appropriate and the patient is benefiting from treatment.

Notes:

Entresto should not be co-administered with either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) due to the angiotensin II receptor blocking activity of Entresto.

- 4.3. The Committee **recommended** that the low priority funding recommendation be reassessed, once Novartis' global trials of sacubitril/valsartan versus valsartan have been published (anticipated for 2019).
- 4.4. The Committee **recommended** that the Cardiovascular Subcommittee of PTAC review this application with respect to determining whether the health benefits reported in the trial were relevant in the New Zealand patient population, and consider whether the proposed Special Authority criteria for sacubitril/valsartan is appropriate.
- 4.5. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 4.6. The Committee noted that Entresto was a fixed dose combination tablet of sacubitril (neprilysin inhibitor) and valsartan (an off-patent angiotensin receptor blocker (ARB)). It noted that valsartan was reviewed by PTAC in 2003 and that it had previously considered that it did not offer additional health benefit compared to other angiotensin receptor blockers (losartan, candesartan) already listed on the Pharmaceutical Schedule.
- 4.7. The Committee considered the treatment algorithm for heart failure currently used in practice. It considered that the usual treatment algorithm consisted of the combination of a loop diuretic, an ACE inhibitor (or ARB if ACE not tolerated), a beta blocker and aldosterone receptor antagonist, and that this algorithm was clinically effective.
- 4.8. The Committee noted that the Supplier had proposed that Entresto be funded via Special Authority criteria for patients with NYHA classes II-IV who have a LVEF of less than or equal to 40% and who are receiving concomitant optimal standard heart failure treatments. It considered that, if sacubitril/valsartan was funded according to the Supplier's proposed Special Authority criteria, it would be used after either an ACE inhibitor or angiotensin receptor blocker had failed in the treatment algorithm. It considered that the use of beta blockers, digoxin, diuretics and mineralocorticoids for heart failure would remain unchanged, and would be used in combination with sacubitril/valsartan.
- 4.9. The Committee noted PARADIGM-HF, a phase III multicentre (984 sites in 47 countries), double blind, randomised controlled trial comparing the efficacy and safety of Entresto to enalapril on morbidity and mortality in 8,399 patients with chronic heart failure and a reduced ejection fraction (N Engl J Med. 2014;371:993-1004). Patients included in this trial included heart failure (NYHA class II-IV), LVEF less than or equal to 40%, B-type natriuretic peptide (BNP) of greater than or equal to 150 pg/ml, heart failure hospitalisation in the past 12 months, previous treatment for at least 4 weeks using an angiotensin

converting enzyme inhibitor or angiotensin receptor blocker at a dose equivalent to enalapril 10 mg, a beta blocker and consideration of an aldosterone antagonist, if indicated. The sacubitril/valsartan versus enalapril hazard ratio for the primary composite end point was 0.80 (95% CI, 0.73-0.87; $P < 0.001$), and for cardiovascular death 0.80 (0.71-0.89; $P < 0.001$). The primary composite outcome of a composite of death from cardiovascular causes or hospitalisation for heart failure, occurred in 914 (21.8%) patients in the Entresto group and 1,117 patients (26.5%) in the enalapril group, hence, Entresto treatment was reported to reduce the risk of death from cardiovascular causes or hospitalisation for heart failure, when compared to enalapril (ARR 4.69% for the composite end point, 3.13% for cardiovascular death alone, 2.8% for first HF hospitalisation alone). Adverse effects: 28% of patients in the Entresto group and 32% in the enalapril group discontinued study medication. As reported in the full clinical study report, the Entresto group had a higher incidence of hypotension and more angioedema events (none with airway compromise), and a lower incidence of renal impairment, hyperkalaemia and cough compared with the enalapril group. The Committee considered that there was a significant proportion of patients with hypotension in the sacubitril/valsartan group (18%) after all patients with adverse events had exited the trial, and that this had clinical implications as it may lead to falls and cognitive impairment in the older adult population.

- 4.10. The Committee considered that the PARADIGM-HF was a large, high quality study that reported evidence of good clinical effect. However, it also considered that the New Zealand population may differ to the trial population as the mean age of patients in the trial was 64 years, although it considered that this age may be more reflective of the Māori and Pacifica population. The Committee considered that the characteristics of New Zealand patients are typically older women with class III or IV heart failure and multiple comorbidities hence, multiple medications. It also noted that the comparator for this trial was 10 mg enalapril once daily, which is not commonly used in the New Zealand setting. As such, the Committee considered that the study end points may not be translatable to a New Zealand population, and **recommended** that this should be reviewed by the Cardiovascular Subcommittee of PTAC.
- 4.11. The Committee considered that the PARADIGM-HF trial demonstrated a clinically relevant reduction in cardiovascular death and heart failure hospitalisation, over current conventional treatment of heart failure with reduced ejection fraction in the study population. The Committee noted that NICE and CADTH suggested restricting this treatment for patients with heart failure and an ejection fraction of less than 35%, and 40% respectively. The Committee considered that a restriction to patients with an ejection fraction of less than or equal to 35% and NYHA class III-IV would reduce the fiscal risk and target patients with a higher health need. It considered that further restrictions could include patients having trialed a minimum of 4 weeks' standard heart failure treatment without clinical benefit (i.e. ACE inhibitor, ARB, in combination with a beta blocker, aldosterone antagonist, etc.) and a specific BNP or NT-proBNP level. The Committee considered that the Cardiovascular Subcommittee should review the proposed restriction criteria for sacubitril/valsartan.
- 4.12. Members considered that should sacubitril/valsartan be funded on the Pharmaceutical Schedule, some clinicians may wish to use it as a first line agent, or in patients with an ejection fraction greater than 40%, and in patients with asymptomatic heart failure, but that these groups were not included in the pivotal trial. The Committee considered that if sacubitril/valsartan was funded for all patients with heart failure, the most appropriate comparator would be the combination of an ACE inhibitor, beta blocker, and a mineralocorticoid. The Committee considered that the cost of sacubitril/valsartan was significantly greater than its comparator(s), and considered that this added expense may not reflect a proportionally increased clinical benefit.
- 4.13. Members considered that the limitations of the available evidence included that it is limited to a single high quality trial, it did not demonstrate that sacubitril/valsartan offered symptomatic benefit over ACE inhibitor treatment for heart failure, and it did not compare sacubitril/valsartan with other agents in the heart failure pathway. Members also

considered that an angiotensin receptor blocker in combination with a neprilysin inhibitor may have a limited benefit in the clinical pathway, given that no studies have been published comparing valsartan versus valsartan with sacubitril.

- 4.14. The Committee considered that it should review the results of the global Novartis trials, in particular those comparing valsartan alone versus valsartan with sacubitril (PARAGON-HF) once these results are available in 2019. The Committee considered that these studies may address questions such as whether the sacubitril/valsartan combination offered additional clinical benefit compared to valsartan alone, any quality of life benefit and further data on the rates of adverse effects (such as, hypotension in older adults). The Committee **recommended** that it reviews its low priority recommendation outlined above, once it reviews further evidence from these trials when published.
- 4.15. Members considered that it would be useful if quality of life data was available for sacubitril/valsartan, particularly as the EQ5D was measured in the pivotal trial but was not reported.
- 4.16. The Committee considered that breathlessness as a symptom of heart failure contributed to a significant reduction in health status and that the health needs of the family/whānau and wider society were similar to other disease states which have breathlessness as a major symptom, such as chronic obstructive pulmonary disease.
- 4.17. The Committee considered that Māori have approximately twice the prevalence of heart failure, experience heart failure at a younger age and have worse health outcomes compared with other New Zealanders (Wall et al., N Z Med J 2013; 126:35-44, and Sopoaga et al., J Prim Health Care 2010; 2:105-10).
- 4.18. The Committee considered that patients with heart failure reporting poor disease specific health status had a 39% increased risk of death (Pocock et al. Eur Heart J 2012;34:1404-13). Members also considered that a 2-state Markov model of US adult patients with a mean age of 63.8 years, calculated that there would be 220 fewer hospital admissions per 1,000 patients treated with heart failure using sacubitril/valsartan compared to enalapril over 30 years (Gaziano et al. JAMA Cardiol. 2016;1:666-72).
- 4.19. Given that sacubitril/valsartan is a tablet formulation, the Committee considered that there are no non-clinical factors that impact on the use of sacubitril/valsartan by the patient, family/whānau or by healthcare workers.
- 4.20. The Committee considered that the uptake figures provided by PHARMAC staff were reflective of potential uptake and that compared to the supplier's model, New Zealand was likely to have a quicker uptake should this treatment be funded. Members considered that given the current treatment algorithm (outlined above) and using the criteria proposed by the supplier, approximately 10% of patients with heart failure may be eligible for the sacubitril/valsartan treatment (Vilela-Martin et al. Drug Des Devel Ther. 2016;10:1627-39).

5. Paliperidone palmitate 3-monthly depot injection (Invega Trinza) for schizophrenia

Application

- 5.1. The Committee reviewed an application from Janssen-Cilag Pty Ltd for the funding of paliperidone 3-monthly depot injection (Invega Trinza) for the treatment of patients with schizophrenia who are stable on paliperidone 1-monthly depot injection.

Recommendation

- 5.2. The Committee **recommended** that paliperidone 3-monthly depot injection be funded, subject to the Special Authority criteria outlined below, only if it was no more expensive on a mg to mg basis compared with paliperidone 1-monthly depot injection and if the

longer-term financial risks (as outlined in the discussion section below) could be addressed, with a low priority.

Initial application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

- 1 The patient has had an initial Special Authority approval for paliperidone once-monthly depot injection; and
- 2 The patient has been diagnosed with schizophrenia (not another psychotic disorder); and
- 3 The patient has received at least four 1-monthly injections of paliperidone once-monthly depot injection (excluding the additional initiation dose for patients who started on paliperidone once-monthly depot using the one-week initiation dosing regimen); and
- 4 At least the last two injections of paliperidone once-monthly injections were at the same dose; and
- 5 The patient has received clinical benefit from, and is considered to be clinically stable on, paliperidone once-monthly injections.

Renewal from any relevant practitioner. Approvals valid for 12 months where the initiation of paliperidone depot injection has been associated with fewer days of intensive intervention than was the case during a corresponding period of time prior to the initiation of an atypical antipsychotic depot injection.

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

Discussion

- 5.4. The Committee noted that paliperidone 1-monthly depot injection was currently funded for patients with schizophrenia or other psychotic disorders who have tried but failed to comply with treatment using oral atypical antipsychotic agents and have been admitted to hospital or treated in respite care, or intensive outpatient or home-based treatment for 30 days or more in the last 12 months.
- 5.5. The Committee noted that paliperidone is the active ingredient of risperidone, which is also funded in tablet, oral liquid and once-fortnightly depot injection form.
- 5.6. The Committee noted that the supplier was seeking funding of paliperidone 3-monthly depot injection for adults with schizophrenia who have been adequately treated with paliperidone 1-monthly depot injection for at least four months, which is the registered indication for paliperidone 3-monthly depot injection in New Zealand.
- 5.7. The Committee noted that the funding application had been reviewed by the Mental Health Subcommittee in November 2016 and that the Subcommittee had recommended that paliperidone 3-monthly depot injection be listed on the Pharmaceutical Schedule only if cost-neutral to the Combined Pharmaceutical Budget.
- 5.8. The Committee noted that the supplier had provided two key phase III trials in support of its funding application.
- 5.9. The first (Berwaerts et al. JAMA Psychiatry 2015;72:830-9) was a randomised, double-blind, placebo-controlled, multicentre, study that compared the safety and efficacy of paliperidone 3-monthly depot injection with placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with paliperidone 1-monthly depot injection for at least 4 months. The study design included 4 phases: a 3-week screening phase, a 17-week open-label transition phase on paliperidone 1-monthly depot injection, a 12-week maintenance phase on paliperidone 3-monthly depot injection, then stabilised patients were randomised to paliperidone 3-monthly depot injection or placebo during an open-ended double-blind phase.
- 5.10. The Committee noted that the results of this study indicated that paliperidone 3-monthly depot injection has an antipsychotic effect in terms of longer median time to relapse

compared with placebo. However, the Committee noted that the study was designed in such a way that it excluded patients from the double blind phase who would have been less likely to benefit from paliperidone 3-monthly depot injection. For example, patients were excluded from the double-blind phase if they had displayed instability long enough to lead to hospitalisation or if they had displayed any sign of lack of effectiveness to paliperidone monthly depot injection. The Committee noted that of 620 patients who were screened, only 506 were enrolled and only 305 of those entered the double-blind phase of the trial.

- 5.11. The Committee considered that the exclusion criteria, for the trial itself and for the double-blind phase, were such that the patient population in the trial was significantly different from the patient population likely to be taking paliperidone depot injection in a New Zealand setting. For example, patients were required to have relatively stable social circumstances and were excluded from the double-blind phase of the trial if they used other licit or illicit psychoactive drugs.
- 5.12. The Committee noted that there was no difference between paliperidone 3-monthly depot injection and placebo for many of the secondary endpoints of the trial.
- 5.13. The Committee considered that this was a weak study in terms of patient selection and design with weak to moderate effects in the primary outcome variable and weak to no effect in the secondary variables, and it was difficult to generalise the results to the New Zealand population.
- 5.14. The second study (Savitz et al. *Int J Neuropsychopharmacol.* 2016;19: pii:pyw018) was a randomised, double-blind, parallel-group, multicentre trial designed to test the non-inferiority of paliperidone 3-monthly depot injection to the 1-month formulation in patients with schizophrenia who were previously stabilised on paliperidone 1-monthly depot injection. The study design included 4 phases: a 3-week screening phase, a 17-week open-label maintenance phase on paliperidone 1-monthly depot injection, a 48-week double-blind phase in which stabilised patients who had responded to paliperidone 1-monthly depot were randomised to paliperidone 1-monthly depot injection or paliperidone 3-monthly depot injection, then a follow-up phase. The primary efficacy outcome was relapse rate at the end of a 48-week double-blind phase.
- 5.15. The Committee noted that the results supported the non-inferiority of paliperidone 3-monthly depot injection to paliperidone 1-monthly depot injection on the primary endpoint: relapse rates were similar in both groups (8% in the 3-monthly group and 9% in the 1-monthly group; difference in relapse-free rate: 1.2% [95% CI:-2.7%; 5.1%]) based on Kaplan-Meier estimates.
- 5.16. The Committee noted that, like the Braewerts study above, the patients who entered the double-blind phase of the Savitz study were more 'well' than would likely be seen in clinical practice in New Zealand. The Committee considered that this study was weak in design but strong in its findings of non-inferiority.
- 5.17. Overall, the Committee considered that the two studies provided a level of confidence that switching patients from paliperidone 1-monthly to 3-monthly depot injection would result in similar clinical (safety and efficacy) outcomes to those seen with paliperidone 1-monthly depot injection.
- 5.18. The Committee noted that the current Special Authority criteria for paliperidone 1-monthly depot injection included patients with "schizophrenia or other psychotic disorders". Given that paliperidone 3-monthly depot injection is only registered for use in schizophrenia, and the clinical trials were conducted only in patients with stable schizophrenia, the Committee considered that it would be important to state in any Special Authority criteria that funding was restricted to patients stabilised on paliperidone 1-monthly depot with schizophrenia, not any other psychotic disorder.

- 5.19. The Committee considered that no evidence had been provided to support an adherence benefit from paliperidone 3-monthly depot injection versus paliperidone 1-monthly depot injection. The Committee noted that in the Savitz 2016 study, adherence appeared similar between the two formulations in the double-blind phase, with about 70% of patients in each group adherent to all depot treatments. The Committee noted that there was no evidence to suggest that efficacy outcomes would improve with the availability of paliperidone 3-monthly depot injection, compared with paliperidone 1-monthly depot injection.
- 5.20. The Committee considered that paliperidone 3-monthly depot injection was unlikely to have a significant impact on secondary mental health services or the number and nature of secondary mental health service contacts with the patient. The Committee noted that there were multiple factors other than the frequency of depot medication administration that would have a much greater influence on the patient's level of contact with secondary mental health services, such as their social circumstances and psychopathology.
- 5.21. The Committee noted that depot antipsychotic administration was only a very small part of the overall cost of care for a patient with schizophrenia and, as such, the availability of paliperidone 3-monthly depot injection was unlikely to result in any significant savings to the health system from reduced medication administration.
- 5.22. The Committee considered that insufficient evidence had been provided to support the supplier's claim that paliperidone 3-monthly depot injection would allow more patients to be managed in primary care. The Committee considered that this would be unlikely to occur to any significant extent if paliperidone 3-monthly depot injection were funded. The Committee considered that paliperidone 3-monthly depot injection would be primarily administered in secondary care settings and in patients' homes by mental health nurses, with occasional patients having administration by primary care nurses in General Practice surgeries to essentially the same degree as paliperidone 1-monthly depot injection.
- 5.23. The Committee considered that the main benefit of paliperidone 3-monthly depot injection over currently available depot antipsychotics is that most patients would prefer to receive, and most clinicians would prefer to give, less frequent injections. The Committee considered that there was no evidence provided in support of switching from paliperidone 1-monthly to 3-monthly depot injection for any reason other than patient preference.
- 5.24. The Committee noted the information provided by the supplier in relation to the impact of paliperidone 3-monthly depot injection on the health need of others; however, the Committee considered that while it would no doubt be welcomed by those involved with the care of a patient with schizophrenia, the availability of paliperidone 3-monthly depot injection would be unlikely to have a significant health benefit for family/whānau or other caregivers.
- 5.25. The Committee considered that if paliperidone 3-monthly depot injection was funded it would likely result in a significant increase in patients being initiated on paliperidone 1-monthly depot injection as a means to eventually transitioning on to a 3-monthly depot preparation. The Committee considered that availability of paliperidone 3-monthly depot injection would also likely lead to patients switching from other depot injections to paliperidone 1-monthly depot injection for the same reason. The Committee considered that the market would shift quite quickly to paliperidone 3-monthly depot injection and the total patient number would quickly exceed the current number of patients on paliperidone 1-monthly depot injection (currently approximately 2,500 patients). The Committee noted that this shift in market dynamics would pose a significant fiscal risk given the large difference in cost between the oral and depot antipsychotics.
- 5.26. The Committee noted and endorsed the comments from the Mental Health Subcommittee in November 2016 that it would be reasonable from a pharmacological viewpoint to apply reference pricing to paliperidone and risperidone depot injections as they are essentially the same chemical and have the same mechanism of action, safety profile and efficacy

outcomes, noting that considerable implementation support would be needed if reference pricing activity resulted in only a fortnightly presentation (risperidone) remaining fully funded given that most patients are now initiated on a monthly presentation (paliperidone). The Committee noted that funding of paliperidone 3-monthly depot injection could potentially have a negative impact on PHARMAC's ability to leverage savings from this type of reference pricing activity as implementation would be more difficult given the likely patient preference for a 3-monthly presentation.

6. Levodopa/carbidopa intestinal gel and its associated pump for Parkinson's disease

Application

- 6.1. The Committee considered an application from Abbvie for the funding of levodopa/carbidopa intestinal gel and its associated pump for the treatment of advanced Parkinson's Disease.

Recommendation

- 6.2. The Committee **recommended** levodopa/carbidopa intestinal gel and its associated pump for the treatment of advanced Parkinson's Disease be listed with a low priority.
- 6.3. The Committee **recommended** PHARMAC consult with the Neurological Subcommittee and the Gastrointestinal Subcommittee regarding specific health-sector expenditure other than for direct treatment costs (e.g. health resource estimates and treatment of side effects associated with the device).
- 6.4. The Committee **recommended** that PHARMAC consider including in its Guidance for Funding Applications a request that when a carer burden scale is provided, suppliers also provide a mapping from that scale onto standard Quality of Life measures, along with evidence for an appropriate level of minimum clinically important difference.
- 6.5. The Committee took into account, where applicable, PHARMAC's relevant decision making framework for these recommendations.

Discussion

- 6.6. The Committee noted that Parkinson's Disease (PD) is a chronic neurodegenerative condition, and that there are currently no treatments to slow or reverse the natural course of the disease. The Committee noted that people with advanced PD experience uncontrolled and unpredictable motor fluctuations, some (with or without troublesome) dyskinesias and have symptoms that are not well controlled with oral symptomatic treatments.
- 6.7. Members considered that about one third of those with PD have marked activity limitations including mobility limitations and that all survivors of PD are likely to progress to severe states within about 12 to 14 years of disease onset. The Committee considered that motor fluctuations including 'off-states' become more common with time; occurring in about 40% of those with treatment by 5 years. Members considered that nearly all PD patients develop dementia if they survive 20 years.
- 6.8. The Committee noted levodopa/carbidopa intestinal gel had an identical mechanism of action to oral levodopa/decarboxylase inhibitors and a similar mechanism of action to dopamine agonists, MAOIs, COMT inhibitors, amantadine and apomorphine infusions. The Committee considered the rationale for benefit with continuous intestinal administration is to bypass variable gastrointestinal absorption to achieve smoother steady state blood and brain dopamine levels which probably contribute to motor fluctuations.
- 6.9. The Committee considered that funded treatment options for advanced PD with severe motor fluctuations in those with intact cognitive function included ongoing expert

medication manipulation, apomorphine subcutaneous infusion, deep brain stimulation (for those with severe disabling tremor), active and ongoing physiotherapy and Multi-Disciplinary Team (MDT) based rehabilitation. The Committee noted that no direct comparative evidence had been provided against any of these treatment options.

6.10. The Committee considered and reviewed evidence, regarding the health benefits and risks, provided by the supplier including the following publications:

- Olanow et al. *Lancet Neurol* 2014;13:141-9. This was a 12 week randomized, double-blind, placebo controlled study evaluating safety and efficacy of levodopa/carbidopa intestinal gel infusion in patients with advanced PD. 71 patients had jejunal placement of a PEG-J tube, and were then randomly allocated (1:1) to receive treatment with immediate-release oral levodopa/carbidopa plus placebo intestinal gel infusion (34) or levodopa/carbidopa intestinal gel infusion plus oral placebo (37). The primary efficacy endpoint was change between baseline and final visit (week 12) in the mean number of Off-hours collected on a home diary during the 3 days before each visit, normalized to a 16h walking day. 31 (out of 34) patients who received levodopa/carbidopa intestinal gel infusion plus oral placebo and 35 (out of 37) patients who received immediate-release oral levodopa/carbidopa plus placebo intestinal gel infusion completed the study and were included in the full data set. The authors reported the active treatment arm to reduce 'off' time by a mean (\pm SE) of 1.91 hours. an estimated time in the 'off phase' improvement, associated with the active treatment arm of 1.9 hours. The Committee considered (from its own calculations, based on standard deviations and sample size) that the likely 95% CI is 0.04 to 3.76 p=0.045. The authors reported a difference, in favour of active treatment, in EQ-5D of 0.07; however, the Committee considered that the study was not sufficiently powered to detect a difference. The Committee noted that approximately 89% of patients had some problem with the PEG-J tube.
- Slevin et al. *J Parkinsons Dis* 2015;5:165-7. An open label extension to the trial described above. The Committee considered, from the adverse event summary, that it appeared 14/55 (25%) of patients who had data had a serious event, that device complications appeared to be with 48 and 58% and that probably around 36/55 (65%) patients were still using the infusion at one year.
- Nyholm et al. *Clin Neuropharmacol* 2003;26:156-63. This was a 3 week randomized cross over trial investigating the pharmacokinetics of levodopa/carbidopa infusion versus oral sustained release tablets in 12 patients. The Committee considered that the results were poorly reported with little identifiable effectiveness data.
- Nyholm et al. *Neuro Pharmacology* 2005;64:216-23. This was a three week randomized cross over study comparing conventional treatment with levodopa/carbidopa intestinal infusion in 24 patients. The Committee noted that the authors reported the mean time in a good state to be about 91% for the infusion and about 75% for conventional treatment. The Committee considered that based on an awake time of 18 hours this would equate to an incremental gain of around 3 hours per day in the "ON" state. The Committee considered that this trial, as with the trial by Nyholm et al. (2005 described above) to also be poorly reported with little identifiable effectiveness data and likely selective reporting of positive outcomes data.
- Antonini et al. *Parkinsonism Relat Disor* 2015;21:231-5. This was a 12-month observational study investigating long-term efficacy and safety of advanced PD patients receiving levodopa/carbidopa intestinal gel infusion, in 172 tertiary centers. The Committee noted that approximately 67% of patients (115 out of 172) were reported to be still using the infusion after 12-months, and that the reduction of mean

daily “Off” time at 12-months was -4.7 ± 3.4 h ($p < 0.0001$). In addition, the Committee noted that PDQ-8 scores (Parkinson’s Disease questionnaire short version with 8 items questionnaire) were reported to have significantly improved; -8.6 ± 22.6 points ($p = 0.0100$) at 12 months. The Committee noted that 37/159 patients (23.3%) were reported to have experienced serious adverse events and that problems with the delivery device appeared to be prominent. The Committee noted that deaths were reported in 15/172 patients (8.7%).

- Lang et al. *Mov Disord* 2016;31:538-48. Safety data from 4 prospective studies was integrated to assess the safety of levodopa/carbidopa intestinal gel. The Committee noted that procedure/device adverse events were reported to have occurred in 300 patients (76%), and serious adverse events occurred in 68 (17%) and that the most frequently reported procedure/device adverse events and serious adverse events were complications of device insertion (41% and 8%, respectively) and abdominal pain (36% and 4% respectively).
- Fernandez et al. *Mov Disord* 2015; 30:500-9. A prospective, 54 week, open-label study on the effects of levodopa/carbidopa intestinal gel in 354 PD patients with severe motor fluctuations. Of the 354 enrolled patients, 272 (76.8%) completed the study. The Committee noted that complication of device insertion (34.9%) was the most common adverse event reported with 7.6% of patients withdrawing because of adverse events. The Committee noted that serious adverse events occurred in 105 (32.4%), most commonly complication due to device insertion. The Committee noted the authors reported a mean daily off time decrease of 4.4 h ($p < 0.001$), a mean change of $+0.064$ units in EQ-5D and 6.9 units in PDQ-39.
- Lundqvist et al. *J Neurol* 2014;261:2438-45. An observational study reporting Quality of Life (QoL), using the 15D, for 10 patients. The Committee noted that the mean QoL scored (15D) improved from 0.63 to 0.70 after three months but went down to 0.66 by 12 months. No confidence intervals were reported.
- Chaudhuri and colleagues and Poewe and colleagues [Chaudhuri 2016 International Congress PD 2009 Abstract, Poewe 2016 International Congress PD 1981 Abstract]. Poster presentations of 24 month follow up data from the cohort of patients investigated by Antonini et al. (*Parkinsonism Relat Disor* 2015;21:231-5) (Described above). The Committee noted that it appeared that of those with data at 24 months ($n = 152$) the mean change reported from baseline in ‘off’ time was ~ 4 hours. The Committee noted that deaths were reported for 29 patients and considered that if the denominator used was 375 patients then this would be about 8% over 2 years.

6.11. The Committee considered the quality of the evidence to be moderate and the strength (effect size of benefits) to be small to moderate compared to oral treatment. In summary, with regards to the health benefits and risks to the person with levodopa/carbidopa intestinal infusion the Committee considered the benefits are increased time out of the off-state, reported as approximately 2 hours per day in the RCTs and 4 hours per day in observational studies. The Committee considered that with regards to QoL there appeared to be a utility change of about 0.07 after 12 weeks, but that this perhaps diminishes over time to 0.03. The Committee considered that approximately 25% of patients have some sort of serious device-related complication and that it is likely that around 66% of patients would still be using the treatment after one year.

6.12. The Committee noted an open-label observational 6-month study comparing 43 patients on apomorphine with 44 patients on levodopa-carbidopa (Martinez et al. *Mov Disor* 2015;30:510-6). The Committee noted that the authors reported that both treatments had similar efficacy on motor scores, no significant differences were detected. The Committee

considered that the evidence provided did not support a health benefit for patients that would choose levodopa/carbidopa intestinal gel over apomorphine, but that levodopa/carbidopa intestinal gel would offer an alternative treatment option for those whom apomorphine was not effective or not suitable.

- 6.13. Members noted that the proposed cost of one year's treatment with levodopa/carbidopa intestinal gel, for the pharmaceutical alone, was similar to the cost of Deep Brain Stimulation (DBS). Members considered that Deep Brain Stimulation was a highly effective treatment in carefully selected patients and that there may be some patients for whom DBS is not suitable but levodopa/carbidopa intestinal gel could be.
- 6.14. The Committee noted a small study by Santos-Garcia et al. (Eur J Neurol 2012;19:1261-5) which prospectively evaluated the quality of life of seven advanced PD patients treatment with levodopa/carbidopa intestinal gel and their caregivers. The Committee noted that the Zarit Caregiver Burden Index and Caregiver Strain Index were used to estimate QoL. The Committee considered that it was unclear how these measures would map to health utility and therefore what clinically meaningful changes would be. The Committee considered that the clinical relevance of the results of this small study were uncertain; however, it considered that there may be reduced carer burden and hence health benefits to the carer as a result of increased ON time. The Committee **recommended** that PHARMAC consider including in its Guidance for Funding Applications a request that when a carer burden scale is provided, suppliers also provide a mapping from that scale onto standard Quality of Life measures, along with evidence for an appropriate level of minimum clinically important difference (MCID).
- 6.15. The Committee noted that due to the progressive nature of the disease patients often require substantial care; commonly provided by the patient's partner or another family member. The Committee considered based on two publications Martinez-Martin et al. (Mov Disord 2015;30:510-6) and Schrag et al. (Parkinsonism Relat Disord 2006; 12:35-41); that overall, care-givers of those with PD appear to experience a decrement in health-related quality of life and this is worse as the severity of PD increases, falling from a utility of 0.8 to 0.64 when disability increases from Hoehn and Yahr (HY) stage III to IV. The Committee considered that as PD disability increases it is likely that more formal support services for a person would be needed. The Committee considered that the quality of the evidence regarding health need is poor to moderate; comprising sample surveys with uncertain sample frames, likely response bias and small samples of very disabled patients. The Committee considered that the strength of the association between worsening PD and disability and poor QoL was high for patients and moderate for care-givers.
- 6.16. The Committee considered the patient population most likely to benefit from treatment with levodopa/carbidopa intestinal gel would be PD patients with severe fluctuations and long off-periods, not controlled with expert medication titration, who are cognitively intact and are able to undergo technical requirements of PEG-J insertion. The Committee considered that patients would require a care-giver to assist with management and any complications of the device, and would need to have access to health-care facilities with expertise in the management of PEG-J tubes and PD. With regards to disease severity the Committee considered that these patients would be stage four or five on the HY scale of PD severity: severe disability but still able to walk or stand unassisted.
- 6.17. Members noted data from a publication by Martinez-Martin et al. (Mov Disord 2015;30:510-6) where the authors reported that based on physician selection approximately half of patients received apomorphine and half received levodopa/carbidopa intestinal gel. Members considered that this would be a reasonable estimate for the numbers of patients who would use levodopa/carbidopa intestinal gel if it were available. Members considered that it seems unlikely that if a patient did not respond to apomorphine that they would respond to the gel but noted that if apomorphine was not tolerated then these patients may then try levodopa/carbidopa intestinal gel if it was available.

- 6.18. The Committee considered, based on a publication by Antonini et al. (Parkinsonism Relat Disor 2015;21:231-5) and a poster abstract by Poewe and colleagues [Poewe 2016 International Congress PD 1981 Abstract] that if levodopa/carbidopa intestinal gel was funded approximately 25-45% of patients would concomitantly take oral levodopa, at approximately 25% of the pre-gel dose. In addition, Members considered that approximately 25% of patients would take other agents in combination with the intestinal gel.
- 6.19. Based on a NZ prevalence survey by Caradoc-Davies et al. (Acta Neurol Scand 1992;86:40-4) and the approximate numbers of patients from PHARMAC data on dispensed dopamine precursor and decarboxylase inhibitors the Committee considered that it is likely that there are around 5000 patients in NZ with PD. Members considered that based on the number of patients accessing apomorphine that there might be about 100 patients who would consider treatment with levodopa/carbidopa intestinal gel if this was a funded option.
- 6.20. The Committee considered that should levodopa/carbidopa intestinal gel be funded that there would be significant consequences to the health system with regards to both resource implications and health sector expenditure. Members considered that it is a technically demanding technology with a high burden of adverse consequences requiring a more intensive monitoring period than apomorphine. The Committee noted that initiation requires several days in hospital with a naso-gastric tube in place to establish dosing and efficacy followed by insertion of a PEG-J tube requiring a gastroenterologist, endoscopy and post-op care, and possible subsequent hospital admissions relating to complications of the PEG-J. The Committee **recommended** that PHARMAC seek advice from the Neurological and the Gastrointestinal Subcommittee regarding specific health-sector expenditure other than for direct treatment costs (e.g. health resource estimates and treatment of side effects associated with the device).
- 6.21. Members considered that theoretically a reduction in OFF time associated with treatment of levodopa/carbidopa intestinal gel could result in a reduction in costs to the health system, via a reduction in formal personal care resource. However, Members considered that no direct evidence to support this had been provided.
- 6.22. The Committee considered the NZ Health Care estimates derived from the Spanish Health Care estimates reported by Valldeoriola et al. (J Med Econ. 2013;16:191-201) seemed to be relatively comprehensive and were likely to be appropriate. Members considered that in New Zealand, geriatricians were likely to be involved with the care of older patients whereas younger patients were likely to be under the care of a neurologist.
- 6.23. With regards to the effect size of treatment for a cost-effectiveness model, the Committee considered the reductions in OFF time, of about 4hours, reported by observational studies was likely to be an overestimate and that the reduction in mean OFF time of 1.9 hours as reported by Olanow et al. (Lancet Neurol 2014;13:141-9) would be more likely. Members considered that in the two-thirds of patients reported to stay on treatment for one-two years that it is likely that this effect size would be sustained. Members considered that as per Lundqvist et al. (J Neurol 2014;261:2438-45) that it was likely that due to the progressive nature of the disease, the EQ-5D improvement would decrease with time, with a mean increment in utility of 0.07 for three months and then falling to an increment of 0.03 by about 12 months.
- 6.24. The Committee considered that a reduction in the OFF-period would not make a difference to the HY scale as the overall rating of disability would remain. The Committee considered that the HY scale may not be an appropriate surrogate for utility. Members considered QALY gains based off estimated gains in ON-periods would be more appropriate for use in a cost-effectiveness model. The Committee considered that no evidence had been provided to support a change in disease progression or life expectancy and therefore including a change in disease progression or life expectancy in the model did not seem appropriate. Members considered a relative risk of progression of 1 would

be appropriate for modelling.

- 6.25. Members noted that the cost-effectiveness model provided by the Supplier assumed incremental gain sustained for 20 years and considered that this appeared to be an overestimate of the benefits associated with treatment. The Committee noted that maximum observation of health gains was ten years. The Committee considered that there would be an initial gain in QoL over 12 months, followed by steady reversion to baseline QoL within 4.5 years. The Committee considered that a model over a 20-year time period may not be appropriate given the maximum observation for time spent on treatment is 10 years and that by 20 years it is likely that all patients would have developed dementia and would therefore be contraindicated to receiving treatment.
- 6.26. Overall, the Committee considered that levodopa/carbidopa intestinal gel and associated pump should be funded with a low priority, noting the high health need of patients with advanced Parkinson's Disease, the quality (moderate) and strength (small to moderate) of the evidence of health benefits to the person, the high cost of the treatment and the high technical failure rate associated with the device.

7. Topical clindamycin vaginal cream for bacterial vaginosis and desquamative inflammatory vaginosis

Application

- 7.1. The Committee considered a funding application from a clinician for the funding of clindamycin vaginal cream 2% for bacterial vaginosis (BV) and desquamative inflammatory vaginitis (DIV).

Recommendation

- 7.2. The Committee **recommended** that clindamycin vaginal cream 2% for bacterial vaginosis be listed with a low priority.
- 7.3. The Committee **recommended** that the application for clindamycin vaginal cream 2% for desquamative inflammatory vaginitis be declined.
- 7.4. The Committee noted there may be a small group of exceptional patients with DIV for whom clindamycin vaginal cream 2% access could be considered on an individual patient basis via the Named Patient Pharmaceutical Assessment (NPPA) policy. The Committee **recommended** that advice about be sought from the Reproductive and Sexual Health Subcommittee (RASH) on the prevalence of DIV, and the need for and benefits of clindamycin vaginal cream 2%.
- 7.5. The Committee also **recommended** that advice be sought from the Anti-Infective Subcommittee on the potential for antimicrobial resistance with topical clindamycin cream for both the BV and DIV indications.
- 7.6. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 7.7. The Committee noted that in November 1998, a funding application for clindamycin vaginal cream 2% for BV was considered by PTAC. Following advice from PTAC, PHARMAC placed clindamycin vaginal cream 2% on a recommended for decline list. PTAC has not previously considered clindamycin vaginal cream 2% for the indication of DIV.
- 7.8. The Committee noted that Dalacin V is the only clindamycin vaginal cream product that has been registered in New Zealand, but has never been funded. Its Medsafe approval

lapsed in November 2011.

Bacterial Vaginosis

- 7.9. The Committee noted that BV is the most common cause of vaginal discharge in women of childbearing age, accounting for up to 50 percent of cases. Approximately 50 to 75 percent of women with BV are asymptomatic. The Committee considered that patients are only likely to be treated if they are symptomatic and current evidence does not support population-based screening and treatment, even during pregnancy. Members noted that BV resolves in up to one-third of women, although over 50 percent of women experience recurrence within 12 months.
- 7.10. The Committee noted that oral metronidazole is the standard treatment for BV in New Zealand, with oral ornidazole being an alternative option (both fully funded). The Committee noted that these oral treatments were associated with high resolution rates. Similarly, in the UK, oral metronidazole is the preferred antibiotic for BV, with clindamycin vaginal cream 2% considered an alternative in patients intolerant to metronidazole.
- 7.11. The Committee noted that the applicant advises that only a few of the 1000 women with BV presenting at New Zealand sexual health services could not be managed with currently available oral metronidazole and ornidazole.
- 7.12. The Committee noted that in a 2009 Cochrane Systematic Review (Oduyebo et al. Cochrane Database Syst Rev. 2009;(3):CD006055) provided high-quality evidence of clindamycin vaginal cream being an effective treatment for BV in symptomatic non-pregnant women. Two trials were found comparing clindamycin cream to placebo (Livengood et al. Obstet Gynecol. 1990;76:118-23 and Stein et al. Ann Pharmacother. 1993;27:1343-5). The Committee noted that compared with placebo, clindamycin showed a lower rate of treatment failure (combined relative risk of 0.25, 95% CI 0.16 to 0.37).
- 7.13. The Committee noted that in the same review, clindamycin vaginal cream 2% and oral metronidazole showed identical rates of BV treatment failure, irrespective of regimen type, at two and four week follow up (RR 1.01, 95% CI 0.69 to 1.46 and RR 0.91, 95% CI 0.70 to 1.18, respectively). Clindamycin tended to cause a lower rate of adverse events (RR 0.75, 95% CI 0.56 to 1.02); metallic taste, and nausea and vomiting were more common in the metronidazole group (RR 0.08, 95% CI 0.1 to 0.59; RR 0.23, 95% CI 0.10 to 0.51, respectively).
- 7.14. The Committee noted that in 1998, when PTAC last considered clindamycin vaginal cream 2%, there may have been some uncertainty about whether oral metronidazole was considered safe during pregnancy. The Committee noted a recent review (Sheehy et al. Curr Drug Saf. 2015;10:170-9) which concluded that metronidazole can be used, is effective, and offers no teratogen risk.
- 7.15. The Committee noted BV during pregnancy has been associated with poor perinatal outcomes and, in particular, preterm birth (PTB). The Committee noted a recent review (Brocklehurst P et al. Cochrane Database Syst Rev. 2013;1:CD000262) concluded that there is little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent PTB and its consequences.
- 7.16. Members noted the population group that may benefit from clindamycin for BV is women intolerant to oral metronidazole but the size of this sub-group is unknown.
- 7.17. The Committee considered that clindamycin vaginal cream 2% would not provide any additional health benefits compared to other funded treatment options for BV. For this reason, if clindamycin vaginal cream were to be listed, it would be a second-line treatment.
- 7.18. The Committee also noted that BV is a recurrent infection so does need to be treated but the Committee considered currently funded oral therapies (such as oral metronidazole) to

be adequate. The Committee considered that given the prevalence of BV and high expected recurrence rates following treatment, if funded, clindamycin vaginal cream 2% may be used widely which may result in considerable additional cost compared to oral treatments.

- 7.19. The Committee considered a Special Authority limiting clindamycin vaginal cream 2% use to women with contraindications or documented intolerance of oral alternatives would be required.
- 7.20. The Committee expressed concerns about the potential for antimicrobial resistance with a new topical clindamycin cream product and requested advice be sought from the Anti-Infective Subcommittee.
- 7.21. The Committee noted there may be an interaction between vaginal cream preparations and latex condoms resulting in contraceptive failure.

Desquamative Inflammatory Vaginitis

- 7.22. The Committee noted that DIV is a rare but chronic clinical syndrome of unknown aetiology but postulated primarily be non-infectious, with secondary bacterial microbiota disruption.
- 7.23. The Committee noted an absence of population-based or primary healthcare-based studies of DIV. One chart review estimated the prevalence of DIV in a specialist vaginitis clinic was 4.3% (Sobel et al. *Obstet Gynecol.* 2011;117:850-5). The applicant advises that approximately 30 cases per year are managed in sexual health clinics around New Zealand, and believes DIV is likely to be poorly recognised outside of sexual health and gynaecology specialities.
- 7.24. The Committee noted that there are no standard treatment interventions for DIV, although hydrocortisone 10% cream (Colifoam rectal foam) may be used intravaginally.
- 7.25. The Committee considered that there is very low quality evidence for the clinical effectiveness of topical clindamycin for DIV. One case series (Sobel JD, *Am J Obstet Gynecol.* 1994;171:1215-20) of intravaginal treatment with 2% clindamycin suppositories showed clinical improvement in more than 95% of patients and, although relapse occurred in 30%, overall antimicrobial cure was achieved in all patients.
- 7.26. Another case series (Sobel JD et al. *Obstet Gynecol.* 2011;117:850-5) of 98 patients found treatment with topical 2% clindamycin (54%) or 10% hydrocortisone (46%) dramatically relieved symptoms within 3 weeks (median) in 86% of patients. Treatment was discontinued (median 8 weeks) in 53 patients experiencing clinical remission, however, 32% relapsed within six weeks. At one year, cure was achieved in 26% of patients, 58% were asymptomatic but remained dependent on maintenance treatment, and 16% were partially controlled only.
- 7.27. The Committee considered that the population group experiencing DIV is small and considered there to be an absence of robust evidence for the use of clindamycin for DIV as no superiority has been shown over other interventions (such as Colifoam). The Committee requested the application for DIV be referred to the RASH Subcommittee for further advice including advice on the prevalence of DIV and the clinical need for other treatment options.
- 7.28. As with the BV indication, the Committee expressed concerns about the potential for antimicrobial resistance, especially in the context of DIV being thought to be primarily an inflammatory condition, and requested advice be sought from the Anti-Infective Subcommittee.

8. Golimumab for moderate to severe ulcerative colitis

Application

- 8.1. The Committee considered the application from Janssen Pharmaceuticals for golimumab (Simponi) for the treatment of moderate to severe ulcerative colitis.

Recommendation

- 8.2. The Committee **recommended** that the application from Janssen Pharmaceuticals for the funding of golimumab for the treatment of moderate to severe ulcerative colitis be declined.
- 8.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

- 8.4. The Committee noted golimumab was first considered by PTAC in May 2010 for the treatment of rheumatoid arthritis and was given a low priority recommendation. Following the listing of etanercept on the Pharmaceutical Schedule in November 2010, golimumab for the treatment of rheumatoid arthritis was re-ranked as neutral/cost saving proposal. In the May 2010 meeting, PTAC also considered and declined golimumab for the treatment of ankylosing spondylitis and psoriatic arthritis on the basis of lack of evidence.
- 8.5. The Committee noted that golimumab was a human IgG1κ monoclonal antibody with high in vitro affinity to soluble and transmembrane TNF-alpha that reduced binding with its receptor; this was considered to be higher affinity than adalimumab and infliximab. The Committee also noted that golimumab is administered subcutaneously via a prefilled pen or syringe at an induction dose of 200 mg followed by 100 mg at week 2 and then 100 mg every 4 weeks thereafter.
- 8.6. The Committee noted that they had previously reviewed and declined the funding of adalimumab for the treatment of the same indication (moderate to severe ulcerative colitis) in November 2013 due to limited evidence for sustained clinical effectiveness, lack of long-term safety data and high financial risk. The Committee also noted that the Gastrointestinal Subcommittee considered a resubmission for adalimumab for this indication in May 2014 and also recommended it be declined. The Committee noted there is currently no available data for golimumab as a second line therapy for patients with ulcerative colitis that have not responded to infliximab.
- 8.7. The Committee noted that the application had requested first line access with the same restrictions as infliximab in the Hospital Medicines List (HML) and listing in the Community Schedule with the same access criteria. The Committee considered that if golimumab was recommended for funding it would be more appropriate as second line after infliximab. The Committee also noted that the currently available monoclonal antibody against TNF-alpha, infliximab, would be considered the comparator. The Committee noted that infliximab is administered via outpatient intravenous infusion every 8 weeks that uses considerable hospital resource whereas golimumab is a subcutaneous injection every 4 weeks that can be administered at home.
- 8.8. The Committee noted there were two main trials for golimumab for ulcerative colitis provided in the submission. The Committee considered the evidence provided was of moderate quality with complex design. The Committee also considered that the trials did not provide data on prior anti-TNF treatment and the relevance to New Zealand was reduced due to a lower percentage of patients receiving immunomodulatory treatment.
- 8.9. The Committee noted the results of the PURSUIT-Induction subcutaneous (SC) trial (Sandborn WJ et al., Gastroenterology 2014;146:85-95) that evaluated the clinical response at 6 weeks in patients with moderate to severely active ulcerative colitis in a double-blind combination Phase 2 (dose finding) and Phase 3 (dose confirming) study. The Committee also noted the results of the longer-term follow up PURSUIT-Maintenance

trial (Sandborn WJ et al., *Gastroenterology* 2014;146:96-109) that evaluated the maintained clinical response of patients at 52 weeks that had initially responded to golimumab in the PURSUIT-Induction trial and were re-randomized to maintenance therapy at doses of 50 or 100 mg.

- 8.10. The Committee noted that while there was some clinical benefit of golimumab for ulcerative colitis compared to placebo at 6 weeks following treatment initiation in the PURSUIT-Induction trial (clinical response in 52-55% of patients, compared to 30% of patients that received the placebo; clinical remission in 18% of patients compared to 6.4% of patients that received the placebo), there was significant improvement over placebo at 52 weeks in the PURSUIT-Maintenance trial 49.7% vs 31.2% ($p < 0.001$). The Committee noted an editorial on the trial (Hanauer, *Gastroenterology* 2014;146:13-5) that reported absolute response rates and showed that of the responding patients re-randomised to maintenance golimumab treatment, 25% maintained a clinical response and 17% attained clinical remission at 52 weeks. The Committee also noted that around 75% of patients in remission at 52 weeks were still on corticosteroids.
- 8.11. The Committee noted that the PURSUIT-Maintenance trial was difficult to interpret due to the inclusion of only patients that responded to golimumab in the induction trial and noted that the initial dose that re-randomised patients received was not stated.
- 8.12. The Committee noted that that (Sandborn WJ et al., *Gastroenterology* 2014;146:85-95) PURSUIT-SC showed that there was a trend to higher response rates at 6 weeks and also clinical remission at 6 weeks with higher serum levels of golimumab. This suggests that there may be a dose response for golimumab although the differences between dosing with 50mg and 100mg were not significant.
- 8.13. Members noted that a meta-analysis of anti-TNF-alpha biologics for ulcerative colitis demonstrated that infliximab had the greatest effect on inducing clinical response or remission (Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy, NICE Technology appraisal guidance [TA329], 2015; <https://www.nice.org.uk/guidance/ta329>).
- 8.14. The Committee compared the clinical response to golimumab to the response observed with adalimumab in the ULTRA2 trial (Sandborn WJ et al., *Gastroenterology* 2012;142:257-65) and noted that the responses were similar.
- 8.15. The Committee noted that meta-analysis reported that 100 mg of golimumab demonstrated better responses in induction than 40 mg of adalimumab in an indirect comparison (Thorlund K., et al., *Expert Rev Gastroenterol Hepatol.* 2015; 9:693-700). The Committee considered that the inclusion of golimumab in the data set required a series of mathematical conversions to account for the different trial design and it was not clear how this was done or how reliable the comparison was.
- 8.16. The Committee considered safety issues from Phase 2 and 3 clinical trials including 5519 golimumab treated patients including 3090 with rheumatoid arthritis, 563 with psoriatic arthritis, 564 with ankylosing spondylitis, 1240 with ulcerative colitis and 231 with severe persistent asthma. Safety was consistent with that reported for other TNF-alpha antagonists and for golimumab in other approved indications.
- 8.17. The Committee noted that the clinical score in the golimumab, adalimumab and infliximab trials were assessed using the Mayo Score, while the Simple Clinical Colitis Activity Index (SCCAI) is used in clinical practice in New Zealand. The Committee noted that patients enrolled in the trials had a Mayo Score of 6, which would correspond to moderate severity ulcerative colitis in New Zealand. The Committee also noted that the rates of immunomodulatory drug use in the trial population were lower than in current New Zealand practice.
- 8.18. The Committee considered there was fiscal risk with adding another treatment option in

ulcerative colitis, given that there is currently no second line biologic treatment. The Committee also considered that there would be a large number of patients that would want to access golimumab after treatment failure with infliximab or those that would consider golimumab a more suitable home based treatment.

- 8.19. The Committee acknowledged that it had reviewed all the evidence provided by the applicant in the application. The Committee considered that this application should be declined on the basis of lack of long-term evidence of sustained clinical benefit.
- 8.20. The Committee noted that there was an unmet clinical health need for patients with ulcerative colitis for biologic pharmaceuticals with a different mechanism of action than the inhibition of TNF-alpha. The Committee requested advice from the Gastrointestinal Subcommittee on whether there was a clinical need for another second-line TNF-alpha inhibitor for ulcerative colitis, or whether there would be preference for an alternative biologic agent.

9. Citrulline for urea cycle disorders

Application

- 9.1. The Committee considered a submission from Orpharma for the funding of citrulline tablets for the dietary management of urea cycle disorders (UCDs).

Recommendation

- 9.2. The Committee **recommended** that the application from Orpharma to fund citrulline tablets (Citrulline Easy tablets) for the dietary management of urea cycle disorders in the Pharmaceutical Schedule be declined.
- 9.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Discussion

- 9.4. The Committee noted the funding application for citrulline tablets for the dietary management of urea cycle disorders (UCDs) is the first supplier schedule application for a treatment relating to the management of urea cycle disorders to be reviewed by PTAC.
- 9.5. The Committee noted the presentation of UCDs and the age of this varies depending on the type and degree of deficit. Patients may be identified by genetic testing or more typically presenting with metabolic decompensation and neurological or gastrointestinal symptoms. If clinical symptoms are present from the earliest days of life, the disorder is usually extremely serious and can be fatal. Members noted that survivors experience severe developmental delay and recurrent hyperammonaemic crises.
- 9.6. The Committee noted that enzyme deficiencies in the urea cycle (with the exception of arginase deficiency) prevent the formation of arginine, rendering it an essential amino acid. Citrulline, an arginine precursor, can be used to supplement amino acids that are depleted with a protein-restricted diet used in the management of UCDs. The Committee noted that the goals of long-term management of UCDs are to achieve normal development and to prevent hyperammonemia (and its resulting short and long term impacts) whilst providing a good quality of life. Members noted that medical management of UCDs usually includes a low protein diet, use of nitrogen scavenger drugs and supplementation of arginine and/or citrulline.
- 9.7. The Committee noted that the nitrogen scavengers sodium benzoate and sodium phenylbutyrate have been recently funded on the Pharmaceutical Schedule following the Medicines for Rare Disorders contestable fund. Arginine powder is available on the Hospital Medicines List (HML) for acute use but community funding would require a NPPA application. Members noted that neither citrulline or arginine are currently funded in the community and have not been considered for a schedule listing. Members noted that

PHARMAC has received a number of NPPA applications for arginine supplementation and a few applications for citrulline for UCDs.

- 9.8. The Committee noted the supplier's application for Citrulline Easy tablets was made on the basis that the tablet formulation may be more acceptable to patients than the citrulline sachets that have been funded on the Pharmaceutical Benefits Scheme (PBS) in Australia since 2010. Members noted the Citrulline Easy tablet submission was recommended for approval in Australia on a cost-minimisation basis compared to the currently listed product. The Committee noted that in New Zealand the application would be more appropriately based on health gains obtainable with citrulline maintenance treatment or a comparison of arginine and citrulline utility.
- 9.9. The Committee noted that the applicant provided no evidence in support of citrulline use and that PHARMAC staff and Committee members had not been able to identify any clinical trials of citrulline supplementation in the management of UCDs. Members noted that research in this area is hampered by it being a rare disease and the treatment being regarded as a dietary supplement and therefore unlikely to realise industry funding for research. The Committee noted PHARMAC provided additional information in support of the application with various observational papers regarding the use of arginine supplementation in UCDs.
- 9.10. The Committee noted European guidelines (Häberle et al. Orphanet J Rare Disease 2012;7:32) consider L-arginine is an essential amino acid in UCDs because of its impaired synthesis and must be supplemented as such or as its precursor L-citrulline. The Committee noted there is a theoretical benefit of citrulline over arginine in improving nitrogen elimination in proximal UCDs but there is no good evidence to support a different impact on patient outcomes and no studies comparing the efficacy of the two supplements (Häberle et al. 2012). Use of arginine and citrulline in UCDs varies worldwide reflecting a lack of consensus on best practice.
- 9.11. Members noted that combination treatment with arginine and citrulline supplementation is also common. A cross-sectional observational study of 208 European patients with non-classical UCDs noted 121 patients with ornithine transcarbamylase deficiency (OTC), which is the most common form of UCD, were treated with either L-citrulline (35%) or with L-arginine (36%) and some patients received both (J Inherit Metab Dis. 2014;37:21–30). Members noted no information on disease progression was reported in this study.
- 9.12. The Committee noted a retrospective questionnaire survey of 43 Japanese patients receiving L-citrulline treatment for a UCD (Tanaka et al. *Pediatr Int.* 2016 Sep 10. doi: 10.1111/ped.13163). Completed patient information surveys were received from 17 institutions covering data from before and after prescription of L-citrulline. The survey included patient background, details of L-citrulline administration, clinical examination data, treatment, frequency of vomiting, and the presence or absence of liver transplantation. Members noted that there were few statistically significant differences in the data reported. Improvements in body weight and protein intake in male OTC patients was reported but the significance of this in relation to L-citrulline intake is unclear. L-Arginine doses decreased significantly with 41% of patients ceasing L-arginine therapy, and 18% having a dose reduction, however, 36% of patients were maintained at the same dose, and in 5% of patients the L-arginine dose increased. Members noted that the serum ammonia levels of patients significantly improved when evaluated at average of 4 months after the initiation of L-citrulline. Unfortunately, the number of decompensation episodes were not reported but it was noted that the 38% of patients with vomiting greater than once per month showed a decrease in the frequency of vomiting (with no data shown). Overall, the Committee considered that the addition of citrulline supplementation may result in improved disease control in comparison to arginine supplementation alone but the impact is uncertain.
- 9.13. The Committee noted a paper by Shchelochkov et al. (*Mol Genet Metab Rep.* 2016;8:43–7) looking at barriers to adherence in the treatment of UCDs suggested that citrulline may

be better tolerated by patients, however this analysis is complicated by low numbers taking arginine. Shcehlochkov et al. estimated that 20–25% of acute hyperammonaemic crises in UCD patients may be related to compliance issues with medications or diet.

- 9.14. Members noted a US survey sent to members of the National Urea Cycle Disorders Foundation to ascertain the types and extent of stress imposed on families who have a child with a urea cycle defect. The greatest sources of stress were financial, fear of death, and the restrictions imposed by the diet (Cederbaum et al. J Pediatr 2001;138:S72-80).
- 9.15. The Committee considered that the patients with UCDs that would benefit the most from citrulline supplementation would be patients with proximal UCDs who cannot tolerate arginine or have insufficient results from arginine alone and are still prone to metabolic decompensation during supplementation with arginine alone. The Committee considered that PHARMAC's estimate of less than 10 patients with UCDs in New Zealand is well informed and appropriate.
- 9.16. Members noted the Citrulline Easy tablets would be suitable for older children able to swallow the tablets whole and could be crushed for use in younger patients. The Committee noted that citrulline and arginine products would be classified as dietary supplements in New Zealand and therefore there was no regulation regarding product quality, safety and efficacy. Members also noted that a dietary supplement should have no stated or implied therapeutic purpose. Members also noted that no information was provided regarding the pharmacokinetics of Citrulline Easy tablets, and considered that this information is required to demonstrate that it would be absorbed and a clinical benefit could be realised.
- 9.17. The Committee noted the high cost per pack for Citrulline Easy tablets, particularly when compared to the cheaper arginine products currently accessed via NPPA. Members noted that PHARMAC has not been able to secure a supply agreement for arginine products previously. Commercial arginine and citrulline products are available in the NZ on the dietary supplement market, however it would be important to ascertain appropriate information regarding good manufacturing practice and quality of these products.
- 9.18. The Committee considered further input from the National Metabolic service would be useful in understanding the need for a funded citrulline supplement in New Zealand, and also for a suitable arginine formulation.
- 9.19. The Committee considered the application for citrulline Easy tablets should be declined based on the lack of evidence to support the use of this particular product in UCDs. The Committee noted the high health need of patients with UCDs with limited available evidence to support different treatment options and noted the rationale supporting the use of arginine or citrulline supplementation to support the management of UCDs. The Committee considered PHARMAC should continue to investigate a suitable source for a pharmaceutical grade preparation of arginine or citrulline that could be considered for funding in the future, however the Committee would require more detailed information addressing the issues discussed above.

10. Allergen pollen extract of 5 grasses for grass pollen allergic rhinitis

Application

- 10.1. The Committee considered an application from Stallergenes for the grass pollen extract of 5 grasses (Oralair) for people over 5 years old, with moderate to severe allergic rhinitis caused by grass pollen, with or without conjunctivitis, who have a positive cutaneous test and IgE titre to certain grass pollens, whose symptoms are uncontrolled on antihistamines and nasal corticosteroids or who are intolerant to symptomatic treatments.

Recommendation

- 10.2. The Committee **recommended** the application to fund the grass pollen extract of 5

grasses (Oralair) for allergic rhinitis desensitisation in adults and children with moderate to severe allergic rhinitis be declined.

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

Discussion

- 10.4. The Committee noted that seasonal allergic rhinitis, or hay fever, is very common in New Zealand, affecting up to 30% of adults and 40% of children. Allergic rhinitis is characterised by symptoms such as sneezing, nasal pruritus, airflow obstruction, and mostly clear nasal discharge caused by IgE mediated reactions against inhaled allergens. Members noted that allergic rhinitis was one of the diseases associated with the atopic march, a series of progressive allergic diseases that include atopic dermatitis, allergic rhinitis, and asthma. The Committee noted the ISAAC (International study of asthma and allergies in childhood) survey that showed slightly higher rates of allergic rhinitis in Maori and Pacific populations compared to NZ European (Moyes et al. *J Paediatr Child Health* 2012;48:913-20).
- 10.5. The Committee noted that the grass pollen extracts in Oralair are from Cocksfoot, Sweet vernal grass, Rye grass, Meadow grass and Timothy and are defined as being 100 IR (Index of Reactivity) or 300 IR per sublingual tablet. They noted that the unit IR (developed by Stallergenes) measures the allergenicity of an allergen extract, where an allergen extract containing 100 IR/ml on a skin prick-test using a Stallerpoint, induces a wheal of 7mm in 30 patients sensitised to this allergen (geometric mean).
- 10.6. The Committee noted a paper by Leynaert et al. (*Am J Respir Crit Care Med*, 2000 :162:1391-6) assessing the quality of life of people affected with AR using the SF-36 quality of life instrument. The authors reported that participants with allergic rhinitis were more likely than subjects with no asthma or no rhinitis to report problems with social activities, difficulties with daily activities as a result of emotional problems, and poorer mental wellbeing.
- 10.7. The Committee noted that there are a range of strategies and pharmacological treatments currently available on prescription and over the counter for the treatment of allergic rhinitis, such as active avoidance of the allergen (though difficult with aeroallergens), oral, intra-nasal, and ocular antihistamines, intra-nasal, and in severe cases courses of oral steroids, mast cell stabilisers and leukotriene receptor antagonists. Members considered that intra-nasal steroids are often painful (and therefore difficult) to administer to children. Members noted that immunotherapy for desensitisation treatment against allergic rhinitis is not currently funded via the Pharmaceutical Schedule, however noted that some District Health Boards currently offer subsidised subcutaneous immuno-desensitisation treatments to some patients although the availability and access to these treatments are variable around the country.
- 10.8. The Committee noted that there are a number of registered allergen immunotherapies currently available in the private market for the treatment of allergic rhinitis in New Zealand, however noted that Oralair is the only sublingual immunotherapy (SLIT) while other registered products are administered as subcutaneous immunotherapy (SCIT). The Committee considered that sublingual immunotherapy (SLIT) would be easier to administer than subcutaneous therapy. They considered that whilst no events of anaphylaxis were reported in the trials for Oralair, the first dose should be taken in a GP practice or specialist setting with resuscitation facilities. Members considered that should this product be funded, it would likely increase the number of GP and specialist visits, particularly as the NZ datasheet indicates that first dose should be taken under medical supervision and that the patient is monitored for 30 minutes.
- 10.9. The Committee noted that for each treatment year, Oralair treatment should be initiated four months before the expected pollen season and maintained until the end of the pollen season. The Committee considered that the duration of pollen season is approximately

four months of every calendar year in New Zealand, meaning that New Zealand patients would be treated for about 8 months of each treatment year. The Committee noted that the supplier indicates that treatment should be continued for three seasons to show maintenance of the effect after treatment cessation.

10.10. The Committee noted the application for Oralair, including the clinical studies provided. In particular, the Committee noted and reviewed:

- Wahn et al., 2009 (J Allergy Clin Immunol 2009;123:160-6), a randomised, placebo controlled trial in children (5-17 years) who received either once daily SLIT tablets (300 IR) or placebo for 4 months before the estimated pollen season and continued throughout the season. The authors reported a statistically different mean difference in rhinoconjunctivitis total symptom score (RTSS) between the 300 IR and placebo groups (-1.13 [95% CI, -1.80 to -0.46]; P=0.001) at the end of the pollen season. The authors found that the 300 IR group showed a mean improvement in the RTSS of 28.0% and a median improvement of 39.9% over placebo, and that the majority of treatment-emergent adverse events were mild to moderate in severity with the most common being oral pruritus, oedema of the mouth, and throat irritation.
- Cox et al., (Journal of Allergy and Clinical Immunology. 2012;130:1327-34), a double-blind placebo-controlled that evaluated the efficacy and safety of 300 IR sublingual tablets in American adults. Adult patients were randomised to either treatment with 300 IR SLIT or placebo commenced 4 months prior to pollen season and continued through the season. The primary endpoint was the daily Combined Score (CS; scale 0-3), which integrates symptoms and rescue medication use. The authors reported the mean daily CS being significantly lower in the active treatment group than the placebo group. The most frequent adverse events were oral pruritus, throat irritation and nasopharyngitis.
- Didier et al., (J Allergy Clin Immunol 2007;120:1338-45), a double blinded, placebo controlled, trial that assessed the efficacy, safety, and optimal dose of grass pollen tablets for immunotherapy of patients (18 to 45 years) with allergic rhinoconjunctivitis. Adults with grass pollen rhinoconjunctivitis received either 100 IR, 300 IR, or 500 IR of the 5-grass pollen extract or placebo, administered sublingually initiated 4 months before the pollen season. The authors found that the treatment effect, assessed as the mean difference in the Rhinoconjunctivitis Total Symptom Score (RTSS) between each active group and the placebo group, was found to be lower in the 300 IR (-1.39 [95% confidence interval (CI) -2.09, -0.69]; P=0.0001) and 500 IR groups (-1.22 [-1.91, -0.53]; P=0.0006) but not for the 100 IR groups.
- Didier et al., 2011 (J Allergy Clin Immunol 2011;128:559-66), Didier et al., 2013 (Clinical & Experimental Allergy, 2013;43:568-77), and Didier et al., 2015 (Clinical and Translational Allergy 2015;5:12), a double blinded, placebo controlled trial that assessed the efficacy of the 300 IR 5-grass pollen allergen sublingual immunotherapy tablet of a 2 dose regimen compared to placebo over three seasons started either 2 or 4 months before the pollen season, and the continued sustained efficacy for up to two seasons after discontinuation of the 300 IR 5-grass pollen allergens. A pre-specified primary outcome measure scored using the Average Adjusted Symptoms Score (AAdSS) was used in Didier et al. 2011 and Didier et al. 2013, but not in Didier et al. 2015, which used the Daily Combined Score (DCS) as its primary outcome measure post-hoc. The authors stated that the reason for this difference was due to the AAdSS being a symptom score that is adjusted by taking into account use of rescue medication, rather than a genuine combined score like the DCS. The authors in the Didier et al. 2011 and Didier et al. 2013 studies reported statistically significant differences in AAdSS in the allergen treated groups (300 IR

2M and 4M pre-pollen season) versus placebo after three seasons on treatment and one season after discontinuation, however Didier et al. 2015 reported a non-statistically significant AAdSS difference in the 300 IR 4 month pre-pollen-season treated group versus with placebo two years after discontinuing treatment. The authors in Didier et al. 2015 reported statistically significant differences in the 300 IR 4 month pre-pollen-season treated group versus placebo using the changed outcome measure Daily Combined Score (DCS) post-hoc, and other secondary outcome measures of Daily Rhinoconjunctivitis Total Symptom Score (DRTSS), and daily rescue medication (DRM) score.

- 10.11. The Committee considered that from a safety perspective, based on the above studies, Oralair tablets were generally well tolerated with the most common adverse events being mild oral pruritus or throat irritation and that no serious systemic events or episodes of anaphylaxis were observed.
- 10.12. The Committee noted that the inclusion criteria in the above studies were those patients who have a grass pollen-related allergic rhinoconjunctivitis for at least the last two pollen seasons (as confirmed by positive skin prick test and IgE level) with a score of at least 12 on the retrospective rhinoconjunctivitis total symptom score (RTSS). The Committee considered that while the baseline characteristics of participants in these trials was reported as being similar, this may not have been an accurate reflection of participant's characteristics as the retrospective RTSS was contingent on recall. The Committee considered that the positive skin prick and IgE tests confirm sensitivity to a particular antigen, however are not predictive of the severity of allergic rhinitis symptoms experienced by the individual.
- 10.13. The Committee considered that overall, the Wahn et al., (J Allergy Clin Immunol 2009;123:160-6), Cox et al., (Journal of Allergy and Clinical Immunology. 2012;130(6):1327-34), Didier et al., 2007 (J Allergy Clin Immunol 2007; 120:1338-45), Didier et al., 2011 (J Allergy Clin Immunol 2011;128:559-66), Didier et al. 2013 (Clinical & Experimental Allergy, 2013;43:568-77), and Didier et al. 2015 (Clinical and Translational Allergy 2015;5:12) studies were large, well powered, and of moderate to high quality.
- 10.14. Noting the studies referenced above, the Committee considered that Oralair's magnitude of benefit and durability of response post treatment were uncertain. The Committee noted the different end-points used across the studies, and specifically the change in the pre-specified end point used in the Didier et al. 2011, Didier et al. 2013, and Didier et al. 2015 studies. The Committee considered that the retrospective rhinoconjunctivitis total symptom score used in the recruitment of trial participants could have introduced recall bias, and that reporting using percentage changes in symptom scores may lead to proportionately larger benefits being reported in those patients with a lower baseline RTSS score. Based on this, the Committee considered that although the health need of patients with seasonal allergic rhinitis was high, they were uncertain that Oralair would lead to an increased quality of life for patients as it was unclear whether the reported benefits would translate into real world benefits.
- 10.15. The Committee considered that there would be a large patient population in New Zealand who may be eligible for treatment with Oralair. The Committee considered that given the long duration of treatment, this may lead to significant budgetary impact risks if this product were to be funded. Members considered that uptake of this treatment would likely be around 15-20% in the first year increasing to around 33% by year 5 if Oralair were to be listed in Section B of the Pharmaceutical Schedule, which is higher than what the supplier has modelled. The Committee considered that the supplier's economic model had assumed a longer benefit than could be supported by the current available evidence, which would likely overestimate the benefit of this treatment.
- 10.16. The Committee considered that a disadvantage of anti-allergen treatments in general, is the length of time patient adherence to treatment is required before a clinical benefit is achieved. The Committee noted that for Oralair, treatment should be initiated four months

before the pollen season and maintained until the end of the season, for three seasons. The Committee noted that while the Didier et al., Wahn et al., and Cox et al. studies had adherence rates generally greater than 90%, that this was unlikely to be reflected the real world setting. The Committee noted a study by Kiel et al., (J Allergy Clin Immunol, 2013;132:353-60) reporting an average of 18% of participants having reached the minimally required duration of treatment of three years with allergen immunotherapies (23% of the subcutaneous allergen immunotherapy (SCIT) and 7% of the sub-lingual (SLIT)). In this trial, median durations for SCIT and SLIT were 1.7 and 0.6 years respectively ($p < 0.001$). The Committee therefore considered that patients taking SLIT are unlikely to finish the full 3-year treatment course, given the long treatment period (at least 8 months of each treatment year) and due to the frequent occurrence of treatment associated adverse events which themselves resemble symptoms of allergic rhinitis.

- 10.17. The Committee considered that whilst there appears to be a correlation of allergic rhinitis with asthma, there is currently insufficient evidence reporting that desensitisation to allergic rhinitis will reduce the incidence of asthma in individuals that are treated with Oralair.