PTAC meeting held on 3 & 4 November 2016

(minutes for web publishing)

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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

Immunisation Subcommittee

1.1. The Committee noted the minutes of the Immunisation Subcommittee meeting held on 23 May 2016.

1.2. The Committee noted items 4.6, 7.5, 7.56 and 8.10 in regard to recommendations made by the Subcommittee to the Ministry of Health.

1.3. The Committee noted and accepted the remaining minutes, with the exception of item 7.54 in relation to the Subcommittee's high priority recommendation to continue funding PCV13 after 1 of July 2017 for vaccination of patients currently defined as being at high risk. The Committee considered that there is little clinically-significant difference between the PCV10 and PCV13 vaccines and that if PCV13 were to remain listed for high risk patients, it should be restricted to the vaccination of those children under 5 years old considered to be at high risk.

Cancer Treatments Subcommittee

1.4. The Committee noted and accepted the minutes of the Cancer Treatments Subcommittee meeting held on 9 September 2016 with the following exceptions.

1.5. Regarding item 4, pemetrexed criteria for mesothelioma and non-small cell lung cancer (NSCLC), the Committee noted that it had previously recommended pemetrexed be funded only if cost-neutral in the first and second-line NSCLC setting and with low priority for the treatment of mesothelioma and as maintenance treatment of NSCLC. The Committee noted and accepted the Subcommittee's recommendations with regards to Special Authority criteria.

1.6. Regarding item 5, PD-1 inhibitors for advanced melanoma access criteria review, the Committee noted that from the current evidence there was uncertainty regarding the optimal use of PD-1 inhibitor treatment. However, accepted the Subcommittee's recommendations with regards to Special Authority amendments.

1.7. Regarding item 6, Targeted treatments for advanced melanoma review, the Committee noted that the recommendations in paragraphs 6.3 and 6.5 related to funding of BRAF/MEK inhibitor treatments for patients with rapidly progressive disease as a bridge to PD-1 inhibitor therapy. This represented a different patient group to that previously considered by PTAC. The Committee noted that no additional evidence had been considered by the Subcommittee at its meeting in September that had not previously been reviewed by PTAC. The Committee requested that this be brought to a future PTAC meeting for review once new evidence was available. The Committee reiterated its previous recommendations that the BRAF inhibitors dabrafenib or vemurafenib as monotherapy or dabrafenib in combination with the MEK inhibitor trametinib be declined.

1.8. Regarding paragraph 7.4 (The Subcommittee's recommendation relating to ibrutinib for patients with 17p deletion or TP53 mutation CLL), the Committee noted that the RESONATE 17 study had since been published and requested that this be brought to a future PTAC meeting for the Committee for review. The Committee deferred making a recommendation regarding funding of ibrutinib for 17p or TP53 CLL pending review of this study. The Committee reiterated its previous recommendations regarding ibrutinib be funded with low priority for the remaining patient populations applied for by the supplier.

Endocrinology Subcommittee

1.9. The Committee noted and accepted the minutes of the Endocrinology Subcommittee

meeting held on 21 June 2016, with the following exceptions.

1.10. Regarding paragraphs 5.5-5.9 (the Subcommittee's review of PTAC's November 2015 and May 2016 reviews of cinacalcet, and its views on cinacalcet), the Committee noted that this would be discussed separately at the meeting under Matters Arising.

1.11. Regarding paragraphs 5.20-5.24 (the Subcommittee's review of PTAC's February 2016 review of micronised progesterone (Utrogestan) and its views on the evidence for this preparation), the Committee noted that the Early Versus Late Intervention Trial with Estradiol (ELITE) trial was conducted using an intrauterine gel and therefore the results were not applicable to oral micronised progesterone, given likely differences in important factors such as absorption and concentration. The Committee considered that the only new evidence cited by the Subcommittee was the Dartois et al. (Int J Cancer 2016;138:2415-27) study. The Committee requested that this be brought to a future PTAC meeting for the Committee for review.

1.12. Regarding paragraph 5.32 (discussion of the Omnitrope brand of somatropin), the Committee noted the statement that Omnitrope was unable to be given to paediatric patients due to the alcohol content and the risk of associated myelin damage. The Committee considered that this did not apply to all paediatric patients i.e. by definition all those up to 18 years of age, noting that the Medsafe datasheet prohibitions and warnings were risks confined to younger patients, and that the datasheet stated that "Because of the presence of benzyl alcohol in the 5mg/1.5mL solution for injection, the product must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old."

1.13. Regarding paragraphs 6.7-6.11 (the Subcommittee's review of PTAC's May 2016 review of denosumab, and its views and recommendations relating to denosumab), the Committee did not agree with the recommendations made by the Subcommittee in relation to the Special Authority criteria proposed by PTAC. The Committee considered that it would be reasonable for applications to be made by any relevant practitioner, noting the relative shortage of relevant specialists. The Committee considered that the proposed wording "patient has had severe adverse reaction to zoledronic acid" in the Special Authority criteria was unnecessarily permissive and imprecise and could result in a large number of additional patients accessing denosumab treatment who could potentially tolerate further zoledronic acid injections. The Committee again recommended that denosumab be listed for the treatment of osteoporosis in postmenopausal women who have received inadequate benefit from oral treatments and for whom zoledronic acid is contraindicated because of renal impairment, with a medium priority, subject to the Special Authority criteria outlined in its May 2016 meeting minutes.

1.14. Regarding paragraph 6.15 (concerns about the excipients in the funded vitamin D preparation), the Committee noted that the currently funded vitamin D preparation (Vit.D3 capsules) contains soya oil, not peanut oil. However, the Committee noted that the Medsafe datasheet lists allergy to peanut or soya oil as a contraindication to this brand.

1.15. Regarding item 7 (somatropin for patients with Prader-Willi Syndrome), the Committee noted that this would be discussed as a separate agenda item.

2. Matters Arising

Cinacalcet

2.1. The Committee noted that in June 2016 the Endocrinology Subcommittee reviewed the minutes of PTAC's November 2015 and May 2016 reviews of cinacalcet.

2.2. The Committee noted the Subcommittee's view that there remained a group of patients

with primary hyperparathyroidism with symptomatic severe hypercalcaemia contraindicated to surgery, or in whom previous surgery had been unsuccessful, and who have an unmet clinical need. The Committee noted the submission from one of the Endocrinology Subcommittee members in support of the funding of cinacalcet for this patient group. The Committee noted the Subcommittee's view that it would be reasonable to extrapolate the evidence for cinacalcet in patients with parathyroid carcinoma to this patient group.

2.3. The Committee appreciated the Subcommittee's and the submitter's concerns, but considered that insufficient new evidence had been provided to support a positive funding recommendation in this patient group. The Committee considered that it was not appropriate to extrapolate the evidence in patients with parathyroid carcinoma, as this was a different disease.

2.4. The Committee again recommended to decline funding of cinacalcet in patients with non-malignant primary hyperparathyroidism with symptomatic hypercalcaemia contraindicated to surgery, or where previous surgery has been unsuccessful.

2.5. The Committee noted that cinacalcet was not funded on the PBS in Australia and suggested that PHARMAC staff conduct further follow-up as to how such patients were managed in Australia.

Antimicrobial Stewardship

2.6. The Committee noted the draft version of the Anti-infective Subcommittee minutes from its October 2016 meeting discussing Antimicrobial Stewardship (AMS), which followed the August 2016 PTAC meeting where, as a result of consultation feedback on an azithromycin proposal, the Committee discussed wider aspects of AMS.

2.7. The Committee reiterated that it takes antimicrobial resistance (AMR) into account when providing advice to PHARMAC, as part of factors considered under PHARMAC's Factors for Consideration decision-making framework.

2.8. The Committee however considered its role was not that of an AMS Committee but rather as making recommendations regarding the funding of antimicrobials (as for other pharmaceuticals) and the settings and indications that funding should apply to. However, the Committee was also aware that, whilst awaiting a national AMS Committee that may be established by the forthcoming national AMR strategy, any recommendations made by PTAC on antimicrobial funding may influence the heath sector's AMS efforts.

2.9. The Committee noted its previous recommendation that PHARMAC should write to the Ministry of Health on the topic of AMS, and requested that this correspondence both convey the current work that PHARMAC undertakes and the advice its Committees provide with respect to AMS and suggest that a Government-mandated national AMS advisory group be established to oversee AMS for the human health sector and make AMS recommendations. The Committee considered that this mandate could be given to PHARMAC or an external group.

3. Correspondence

Micronutrients for people with ADHD

3.1. The Committee noted correspondence from the applicant in relation to PTAC's consideration of a funding application for micronutrients for the treatment of attention deficit and hyperactivity disorder (ADHD). The Committee noted the applicant's disappointment with PTAC's comments and recommendation to decline the funding application.

3.2. The Committee noted and accepted the applicant's explanation as to how blinding of the placebo-controlled trials was achieved despite the pungent odour of the micronutrient products, and considered this issue had been addressed appropriately to the extent possible.

3.3. The Committee noted that it would be happy to reconsider an application should further robust placebo-controlled trial publications become available that were suitably powered over a suitable timeframe with a well-described product.

Polypills

3.4. The Committee noted that at its February 2016 meeting, the Cardiovascular Subcommittee discussed a PHARMAC staff-initiated paper on the wider topic of fixed dose combination polypills, and at that time also reviewed a submission for Trinomia, a fixed dose combination polypill branded formulation (combining aspirin 100mg, atorvastatin 20 mg, ramipril 2.5mg).

3.5. The Committee noted that, in response to the Cardiovascular Subcommittee's review of Trinomia, a letter had been received from the group of researchers who were authors of a New Zealand-based pragmatic randomised controlled trial using a different fixed-dose polypill than Trinomia, and that letter was also endorsed by a number of other clinicians.

3.6. The Committee noted that there were two published studies cited in this letter that had not been previously reviewed by the Cardiovascular Subcommittee at its February 2016 meeting, these being:

- Webster et al. Int J Cardiol. 2016;205: 147-56
- Selak et al. Eur J Prev Cardiol. 2016;23:1537-45

3.7. The Committee noted that the supplier of Trinomia, Te Arai BioFarma, had also submitted the following published studies as late correspondence to PTAC, and the Committee reviewed them in relation to whether they reported clinically relevant cardiovascular outcomes:

- Yusuf et al. N Engl J Med 2016;374:2021-31
- Kim et al. Hypertension. 2016;67:506-12
- Lavikainen et al. BMJ Open 2016;6:e011306

3.8. The Committee noted Webster et al. (2016), a meta-analysis pooling data from the IMPACT, Kanyini-GAP and UMPIRE trials, and noted that the individual trials themselves had been reviewed by the Cardiovascular Subcommittee meeting in February 2016.

3.9. The Committee noted Selak et al. (2016), which assessed clinical outcomes in general practice settings with either of two polypills (combining aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg; or combining aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg) versus usual care, randomised 1:1. The Committee considered that its study design conferred limitations in its interpretation, including the lack of blinding meaning that both groups could not be assumed to be equivalent.

3.10. Members noted the supplementary appendix of Selak et al. (2016) and considered that it reported the reasons study participants cited for not adhering to treatment were primarily lifestyle factors, not the number of pills or the cost. Members also noted in Selak et al. (2016) that the participants did not have the same baseline characteristics, particularly that they were not all currently taking all the polypill agents individually prior to the start of the trial, and although this trial reported the prescribers had agreed that all the individual polypill agents would be appropriate for that patient participant, they did not have to commence patients on those agents at the start of the trial. Given this,

Members considered that the trial did not differentiate between patients who were not prescribed these agents, and patients who did not adhere with prescribed treatment.

3.11. The Committee compared the aggregate cost of the individual treatments with the cost of these treatments in a single pill (a polypill), and considered that when the cost of the polypill is greater, the health outcomes of spending this additional amount should be clear and supported by evidence. The Committee noted that with individual treatments, multiple prescription charges for each individual medicine may render total costs higher, and that this could require further cost minimisation analysis comparing polypill costs with the individual treatments once including prescription charges at a DHB level.

3.12. The Committee considered that, generally, polypills may, in real life, be used widely to treat people who are at low and medium risk of cardiovascular disease, and that the evidence reviewed (listed above) did not demonstrate that there a clear health benefit in these populations. The Committee considered that exposure to increased adverse effects due to the combination of treatments being administered without good evidence of clinical benefit is unnecessary.

3.13. The Committee considered that polypills may lead to an overtreatment of cardiovascular disease in certain populations, for example, in the elderly. The Committee considered that polypills do not allow titration of dosing, due to one of their main features being that they are fixed dose combinations, and Members considered that the overall health outcomes, such as the health and financial cost of older adults having increased falls due to the effects of polypharmacy, needs to be taken into account when considering the benefits of fixed dose combination pills. In addition, the Committee noted that in the meta-analysis reported by Webster et al. 2016 (IMPACT, Kanyini GAP and UMPIRE trials), people who were at increased risk of adverse drug reactions i.e. those in the older adult age group (80-90 years of age), were not included as participants in this trial. The Committee noted that the average age of participants in these trials was between 59-64 years.

3.14. The Committee noted the prescription part charge ($5 per prescription) and that after the twentieth subsidised item in a year per family there was no charge to that family. Members considered that PHARMAC should consider the impact of multiple copayments on patients who are required to collect prescriptions for standard combinations of medications which are also available in a fixed dose combination polypill, for example, where a statin, an ace inhibitor and aspirin are commonly taken to reduce cardiovascular risk. The Committee considered in this instance, where patients are required to pay multiple copayments, PHARMAC staff should consider working with others in the health sector to derive mechanisms to consolidate the copayments, so patients only have to pay once.

3.15. The Committee noted the points in the clinician letter and the additional evidence cited, including the evidence submitted by the supplier Te Arai BioFarma as late correspondence, and reiterated its previous advice, conveyed in its August 2016 minutes, was unchanged.

Pulmonary Arterial Hypertension Treatments

3.16. The Committee noted the correspondence received from the Pulmonary Arterial Hypertension (PAH) Panel dated August 2016 and September 2016, and reviewed its comments regarding the clarifications that PTAC had requested (when PTAC in May 2016 had reviewed the funding application requesting amendments to the current PHARMAC eligibility criteria for the treatment of PAH). This application (reviewed by PTAC in May 2016) had requested a number of changes related to the widening of access of PAH therapies.

3.17. The Committee considered that its recommendations from May 2016 should stand,

except for its recommendations regarding triple therapy for patients with PAH, dual therapy for patients unable to take sildenafil or other phosphodiesterase therapy, and goal directed therapy (May 2016 PTAC minutes: sections 8.3, 8.5 and 8.6) and considered that these should be revised.

3.18. The Committee noted that at its May 2016 meeting, it had requested further evidence from the PAH Panel regarding a number of recommendations, outlined below. The PAH Panel, through this correspondence item, sought to address each of these recommendations or deferrals made by the Committee:

- Regarding goal directed therapy (section 8.3): "The Committee deferred making a recommendation on the use of a goal-directed therapy approach and asked the PAH panel to provide PTAC with more direct evidence to support its use, and in particular assessment of cohort studies or randomised trials of this approach."
- Regarding dual therapy for patients with PAH that are unable to take sildenafil or other phosphodiesterase therapy (section 8.5): "The Committee recommended that the PAH Panel provide PTAC with an assessment about the evidence-based restriction criteria that might be used to determine the approach to dual therapy for patients who are unable to take sildenafil or other phosphodiesterase therapy."
- Regarding triple therapy (section 8.6): "The Committee deferred making a recommendation for the application to fund triple therapy, pending additional evidence and asked the PAH panel to provide PTAC with direct evidence to support its use and in particular assessment of cohort studies or randomised trials of this approach."

3.19. The Committee noted that PAH Panel members had a number of roles: to advocate for their specialist patient group (people with PAH), represent the views of the PAH specialist community, and also provide advice to PHARMAC, using their knowledge of the evidence base for PAH therapy and their clinical practice in this area.

3.20. The Committee noted the advice from members of the PAH Panel that the joint European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines (Galie et al. Eur Heart J 2016;37:67-119. are the most up-to-date source of evidence regarding the treatment of PAH, and that PAH Panel members had stated they were not aware of other evidence additional to these ESC/ERS guidelines. The Committee noted and reviewed the US guidelines referenced in the PAH Panel's correspondence (Taichman et al. Chest. 2014;146:449-75. doi:) and noted this paper consisted of graded consensus statements.

Functional Class II disease at the time of diagnosis

3.21. The Committee had noted at its May 2016 meeting that the current PHARMAC eligibility criteria (http://www.pharmac.govt.nz/2013/03/06/SA1293-PAH.pdf) for funded treatment of PAH therapy allows treatment for patients with PAH in NYHA/WHO functional class II with clear evidence of disease progression, or functional classes III or IV. The Committee had also previously noted at its May 2016 meeting that the application was to widen access to all functional class II patients with PAH at the time of diagnosis, not only those in FC II with clear evidence of disease progression.

3.22. The Committee noted the evidence regarding treatment of PAH in patients who have NYHA/WHO Functional Class II disease (FCII) at time of diagnosis, and noted that the PAH Panel considered that the ESC/ERS guidelines are the most up-to-date evidence for determining the treatment of PAH FCII at the time of diagnosis. The Committee noted that the references contained in the ESC/ERS guidelines, and the ESC/ERS guidelines themselves, had already been reviewed by PTAC in May 2016. The Committee considered that its May 2016 recommendation, of low priority for the funding of Pulmonary Arterial Hypertension treatments in all patients with PAH in NYHA/WHO Functional Class II, should remain unchanged, because the currently

available evidence reported a small clinical effect and no evidence of improvements in overall survival.

Goal directed therapy

3.23. The Committee had noted at its May 2016 meeting that the current PHARMAC eligibility criteria (http://www.pharmac.govt.nz/2013/03/06/SA1293-PAH.pdf) for funded treatment of PAH therapy allows renewal of Special Authority applications for patients who have remained stable or improved on PAH therapy, and that the eligibility criteria allow escalation of treatment to combination therapy for patients who are stable for six months and who then deteriorate (determined by either right heart catheterisation, decrease in 6-minute walk distance, or having PAH in NYHA/WHO functional class IV).

3.24. The Committee noted that the application reviewed at its May 2016 meeting was requesting that patients with FC II, and FCIII/IV PAH be given access to goal-directed therapy. The Committee noted that at its May 2016 meeting, PTAC had deferred making a recommendation due to a need for direct evidence to support the use of goal directed therapy (section 8.3).

3.25. The Committee noted the Panel's evidence for the use of goal-directed therapy reviewed at this November 2016 PTAC meeting. Members noted that the evidence consisted of the ESC/ERS guidelines and the references cited within these guidelines. The Committee noted that the ESC/ERS guidelines use the phrase 'goal-orientated therapy', however, the Committee presumed that goal-orientated therapy and goal-directed therapy are synonymous.

3.26. The Committee noted the view of the PAH Panel that deterioration in right heart function begets further deterioration in PAH, and that the preservation of right heart function was the basis of the Panel's request to initiate treatment earlier, and the request to move to earlier dual and perhaps triple therapy. The Committee reiterated its previous view that there was little direct evidence supporting 'goal-orientated therapy', and that, from the evidence that is currently available, there is insufficient evidence to conclude that treatment targeting particular goals, as cited in the ESC/ERS guidelines, improves survival.

Dual therapy for patients with FCIII or FCIV PAH who have trialed monotherapy for 3-6 months

3.27. The Committee had previously noted at its May 2016 meeting that the current PHARMAC eligibility criteria (http://www.pharmac.govt.nz/2013/03/06/SA1293-PAH.pdf) for funded treatment of PAH therapy does not allow dual therapy unless a patient has had a trial two monotherapies. They noted that in the PHARMAC eligibility criteria that sildenafil must be tried first, except in children with idiopathic pulmonary hypertension secondary to congenital heart disease.

3.28. The Committee noted that in May 2016 that it recommended funding of Pulmonary Arterial Hypertension treatment for patients with PAH in NYHA/WHO Functional Classes III and IV for access to dual therapy following 3 to 6 months of sildenafil monotherapy be given a high priority.

3.29. The Committee noted the evidence presented in the correspondence regarding dual therapy in patients that are unable to tolerate sildenafil, and noted that this evidence consisted of two studies referenced in the ESC/ERS guidelines Hoeper et al. ERJ 2006 4:691-4; McLaughlin et al. Am J Resp Crit Care Med 2006;174:1257-63. The Committee noted that there were two studies in the ESC/ERS guidelines that discussed the use of bosentan/inhaled iloprost, giving this combination a grade IIB recommendation. The Committee noted (from Table 21, page 27 of ESC/ERS guidelines) that these randomised controlled trials (RCTs) did not include patients who could not tolerate PDE-5 inhibitors, but were comparing the combination of bosentan and iloprost against bosentan alone (Hoeper et al. 2006; McLaughlin et al. 2006d).

Both trials were primarily conducted in Functional Class III (FCIII) patients (McLaughlin et al. having one patient in FC II). Hoeper et al. (2006) reported no significant difference in six minute walk distance (6MWD) in participants taking combination treatment (bosentan and iloprost) versus bosentan alone; McLaughlin et al (2006) reported a 24 metre difference in 6MWD, but an improvement in functional class, however, the Committee noted that these results did not provide a confidence interval for the combination therapy. The Committee considered that there was no direct evidence that in those patients who are unable to tolerate sildenafil, that combination therapy with agents in the Endothelin Receptor Agonist such as ambrisentan or bosentan, and Prostacyclin analogue pharmacological classes offered a substantial increase in 6MWD. The Committee also considered that there was no evidence provided to suggest that an increase in 6MWD correlated with an increased health benefit in patients with PAH. The Committee noted the reported improvement in functional class in patients on dual therapy compared to mono therapy in the McLaughlin study: 34% of patients on dual therapy were reported to improve, compared to 6% in monotherapy group, absolute difference 28% (95% CI 10 to 47).

3.30. Based on the above evidence, the Committee recommended dual therapy for patients with PAH in NYHA/WHO functional classes III and IV, who have been taking bosentan or ambrisentan as a monotherapy for 3-6 months (ie. the group of patients that could not tolerate PDE-5 inhibitors such as sildenafil, or in whom PDE-5 inhibitors are contraindicated as a first line treatment), be given a high priority.

3.31. The Committee considered that the targeted access of agents to treat PAH could be via Special Authority criteria which would reduce the administrative burden on clinicians. The Committee considered that the Special Authority criteria may address which patients or group of patients are eligible to move to dual therapy after a trial of monotherapy, for those patients with Functional Class III or Functional Class IV PAH. The Committee also considered that Special Authority criteria may also be useful for targeting which patients with Functional Class II PAH are eligible to move to dual therapy after a trial of monotherapy.

3.32. The Committee considered that one approach for recommending Special Authority criteria for the treatment of PAH would be for the Cardiovascular and/or Respiratory Subcommittee/s of PTAC to undertake a review of the available evidence and following these Special Authority criteria being proposed; it should then be reviewed by PTAC.

Triple therapy in patients with FCIII or FCIV PAH who have trialed dual therapy

3.33. The Committee noted that the current PHARMAC eligibility criteria (http://www.pharmac.govt.nz/2013/03/06/SA1293-PAH.pdf) for funded treatment of PAH therapy does not allow for triple therapy to be prescribed. The Committee had previously noted at its May 2016 meeting that the application was for triple therapy to be available for patients with PAH who had trialled dual therapy, and that at the same meeting the Committee had requested further evidence to support the use of triple therapy. The Committee noted the advice in the correspondence from Members of the PAH Panel, that the ESC/ERS guidelines and the references cited in these guidelines were the most up-to-date evidence.

3.34. The Committee noted that there was only one paper cited in the references of the ESC/ERS guidelines which related to triple therapy (Sitbon O et al. ERJ 2014;43:1691-7). The Committee noted that this paper described a retrospective cohort study of upfront triple therapy of sildenafil, bosentan, and intravenous epoprostenol in 19 patients with very severe PAH. The Committee noted that the study was not randomised and the authors did not report why these patients were placed on triple therapy rather than an initial trial of dual therapy.

3.35. Based on the available evidence, the Committee recommended that the application for triple therapy in patients with PAH be declined, except in the situation where patients

were on an active transplant list. The Committee considered that this patient group had a greater potential to benefit from treatment and therefore recommended that triple therapy for patients with PAH who are on the active lung transplant list be funded with a high priority.

3.36. The Committee considered that there would be considerable fiscal risk in moving to 'triple-therapy' without more robust evidence of survival benefit and therefore certainty of health gain. The Committee considered that should more evidence for the use of triple therapy in treatment of PAH become available, that its recommendation for triple therapy in patients who are not on the active transplant list would need to be reviewed.

4. Adalimumab for severe hidradenitis suppurativa

Application

4.1. The Committee noted a submission from Abbvie for the widening of access of adalimumab to treat hidradenitis suppurativa in patients with severely active hidradenitis suppurativa (HS).

Recommendation

4.2. The Committee **recommended** adalimumab for hidradenitis suppurativa to be listed with a low priority.

4.3. The Committee **recommended** the Special Authority to be defined by the Dermatology Subcommittee at its next meeting.

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

Discussion

4.5. The Committee noted that hidradenitis suppurativa (HS) is a chronic skin disease with variable clinical presentations. Members noted patients with moderate to severe disease have a high health need as it is both a chronic and a disabling disorder and could have psychological consequences because of the appearance of the disease. Members noted these patients developed inflamed abscesses, sinus tracts and scarring; frequently causing keloids, contractures, and immobility.

4.6. The Committee considered HS was due to an underlying inflammatory process and presented primarily in the axillae, under the breasts (in women), inner thighs, groin and buttocks. Members noted HS usually occurs in otherwise healthy adolescents and adults, and is characterised by comedone-like follicular occlusion, chronic relapsing inflammation, mucopurulent discharge, and progressive scarring. Members noted that prevalence was higher in females than in males (female to male ratio, 3:1), and females were more likely to have genitofemoral lesions.

4.7. The Committee considered that the prevalence of HS was 1% of the population but it was unsure about the proportion that would have mild to moderate disease, as many of those patients may either be misdiagnosed as simple boils/abscesses or undiagnosed. Members noted patients suffering from HS had mean time to diagnosis of seven years.

4.8. The Committee noted that the disease had not been well studied prior to 2010. Members noted that a number of prevalence and quality of life studies have been published over the last few years, and that this coincided with the supplier's registration of adalimumab in HS.

4.9. The Committee noted that severe HS had a significant impact on a patient's quality of life when compared to the general population. Members noted HS was associated with obesity, smoking and diabetes. Members noted that patients with severe disease

would require family or care giver support given the possible effects on mobility.

4.10. The Committee noted that pain, odour and immobility were the significant issues experienced by patients with HS. Members also noted the disease had a significant effect on a patient's mental health with around 40% of patients presenting with depression due to disfigurement, reduced mobility, impaired interpersonal relationships and unemployment. The Committee noted the HS had a very high disease burden compared to other dermatological conditions, similar to hirsutism, and erthropoietic protoporphyria.

4.11. The Committee noted that there were various ways of assessing disease severity and response to treatment. The Committee noted the Sartorius grading system, Hurley disease staging classification by Horváth, (Barbara, et al. Acta dermato-venereologica (2016) doi: 10.2340/00015555-2513), and Dermatology Life Quality Index (DLQI) were currently the most robust way of measuring severity of disease. Members noted that DLQI was a well-established instrument that gives the patient's perspective on disease burden. Members noted that the original Hurley classification divided the disease into 3 categories by type of lesion(s) present, but did not take into account extent of disease or disease activity, which the modified Hurley does.

4.12. The Committee noted that pharmacological options for patients with severe disease remained limited and that there was no internationally agreed treatment algorithm for the treatment of HS. The Committee noted that surgery is currently the gold standard of treatment, and other treatments included topical clindamycin 1%, oral antibiotics (tetracycline's, clindamycin, and/or rifampicin), hormonal therapies in women (antiandrogens), corticosteroids (oral and intralesional), and systemic retinoids (isotretinoin and acitretin). Surgical therapies included de-roofing, laser, local excision for milder to moderate disease and wide surgical excision for severe disease. Members noted non-pharmacological therapies included weight loss and quitting smoking. Members considered there was little evidence to show that oral immune suppressants had any effect.

4.13. The Committee noted Hurley I disease is currently largely being managed in primary care and there was no evidence provided by the supplier to suggest that biologic agents are effective in this grade disease.

4.14. The Committee noted studies supplied by the applicant and PHARMAC including (but not limited to):

- Kimball AB et al. N Engl J Med 2016;375:422-34 a study composed of two phase 3 double-blind trials (n=633) evaluating the efficacy and varied dosing response of adalimumab used to treat moderate to severe hidradenitis suppurativa;
- Kimball AB et al. Ann Intern Med. 2012;157:846-55 a phase two, two parallel, randomised control trials for patients with moderate to severe HS who were unresponsive or intolerant to oral antibiotics;
- Miller I et al. BJD. 2011;165:391-8 , a phase 2 randomised, blinded, placebo-controlled trial (n=21) with moderate to severe HS defined as Hurley stage II or III for at least 6 months.

4.15. The Committee considered the evidence was of moderate quality, and low in strength. Members considered the study's population baseline characteristics in the Kimball AB et al. 2016 study were similar to New Zealand patients with HS.

4.16. The Committee noted that there was some uncertainty with the response rate of patients achieving the primary outcome in the adalimumab weekly group compared to placebo in Kimball AB et al. 2016 (Pioneer I and II), Members considered that the 12 weeks response rate to treatment was around 50%. Members considered that patients who did not respond to treatment after 12 weeks, should not continue treatment as

long term response rates did not improve with continued treatment in the PIONEER I and II trials. Members considered that adalimumab's clinical benefit may begin to wane after 3-5 years due to development of anti-adalimumab antibodies as seen in treatment studies of this agent in psoriasis.

4.17. The Committee noted that there was uncertainty over adalimumab treatment's ability in achieving clinical meaningful secondary outcomes in Kimball AB et al. 2016. Members noted adalimumab treatment in PIONEER I did not show clinically significant improvements compared to placebo in secondary outcomes including: NRS30; reduction in total abscess and inflammatory nodule count (AN count) of 0, 1 or 2; modified Sartorius score; and complete eliminations of lesions

4.18. The Committee considered a reduction of DLQI score by 4 to be clinically meaningful and significant, particularly if the total DLQI dropped below 10. However, PIONEER I and II did not show clinically significant improvements in DLQI measures in patients treated with adalimumab. Members noted changes in EQ-5D in from baseline to 12 weeks reported no differences in improvement in the adalimumab group compared to the placebo group.

4.19. The Committee considered the duration of the studies were short in relation to what is a long-term disease. Members noted significant uncertainty with adalimumab's long-term effectiveness for HS, and that there was a high discontinuation rate as reported in the studies. Members noted that the placebo patient groups had significantly higher BMI than the treatment group – with BMI considered to be an important risk factor for this disease.

4.20. The Committee considered the use of placebo as the comparator by Kimball AB et al. (N Engl J Med 2016;375:422-34) may not have been a relevant comparator in the NZ situation as the current standard of care in this situation is surgery. Members noted that although current access to surgery is limited, the comparator could also have been clindamycin and rifampicin combination.

4.21. The Committee noted it would be useful for the supplier to submit long-term follow-up data of the studies. Members also noted that the supplier application did not include the supplementary tables/materials associated with the papers describing the pivotal trials (namely Kimball AB et al. N Engl J Med 2016;375:422-34).

4.22. The Committee noted the European S1 guideline (Zouboulis CC et al. JEADV 2015; 29: 619–44) and a Cochrane systematic review (Ingram JR et al. Cochrane Database of Systematic Reviews 2015;10: CD010081). Members noted the European guidelines and Cochrane review both stated that infliximab and adalimumab would have a similar efficacy for this indication. Members considered infliximab could be slightly more effective than adalimumab due to the higher dosing and its route of administration i.e. IV infusion, but noted infliximab is currently not funded or registered for HS in New Zealand and would require infusion services.

4.23. The Committee considered adalimumab would be easier to administer than infliximab as it is a self-administered SC injection and may free up hospital resources by reducing the need for surgery or admission. However the members noted that the supplier had provided no evidence about this potential offset in use of other resources and that it was difficult to provide an estimate of these potential savings. Members noted that the proposed weekly dosing regimen of adalimumab was higher than for other indications (usually fortnightly), and questioned in a real-life setting whether patients would adhere to the weekly dosing, and if they did not this would likely result in a lower response rate.

4.24. The Committee noted evidence for adalimumab in the treatment of HS focused on patients with Hurley stage II and III disease. Members considered the evidence for

adalimumab in Hurley stage III disease was unconvincing and that there is currently no well-established and robust clinical instrument to measure the effectiveness in severe disease. Members noted that scarring has a significant impact on a patient's mental well-being. Members considered that there was no evidence that treatment with adalimumab would improve established scaring.

4.25. The Committee noted a modified Hurley Staging system by Horváth, Barbara, et al. Acta dermato-venereologica (2016) doi: 10.2340/00015555-2513 would be suitable for assessing patients' eligibility and noted adalimumab should only be available for HS patients with modified Hurley 1C, 2B or 2C.

4.26. The Committee considered the use of adalimumab in HS would primarily be for two indications: 1) as a long-term therapy, as per the supplier's dosing indication, or 2) as a short term bridge to surgery.

4.27. The Committee noted that the supplier had submitted applications to many drug evaluation agencies. Members noted NICE was of the opinion that there was uncertainty if the results had clinical importance. Members also noted the application had been declined by the PBAC in March and July 2016. Members were in agreement with other agencies on the significant uncertainty around long-term effectiveness of adalimumab in HS and the high discontinuation rates as evidenced in the trials provided.

4.28. The Committee noted other biologics including etanercept, ustekinumab, secukinumab and anikinra – all of which had been tried for HS. Members considered that that evidence shows that etanercept had little to no effect to support its use in this indication. Members noted the body of evidence for newer biologics is growing.

4.29. The Committee noted the budget impact analysis and cost-effectiveness analysis submitted by the supplier. Members considered there is significant fiscal uncertainty with listing this product due to slippage. Members considered the budget impact analysis provided by the supplier was an approximate crude estimate. Members considered the cost-effectiveness to be poor with significant uncertainty regards any long-term benefits. However, members considered the indication of HS to be of high clinical need.

5. Tocilizumab for the treatment of cytokine release syndrome

Application

5.1. The Committee reviewed an application from a clinician for the funding of tocilizumab for the treatment of cytokine releasing syndrome (CRS) associated with the administration of blinatumomab for the treatment of acute lymphoblastic leukaemia (ALL) for patients being treated as part of the Children's Oncology Group AALL1331 trial. The Committee also reviewed a request from PHARMAC staff to consider widening access to tocilizumab for the treatment of CRS associated with any treatment associated with a high risk of CRS.

Recommendation

5.2. The Committee **recommended** that the application to widen access to tocilizumab for the treatment of cytokine release syndrome in Section H of the Pharmaceutical Schedule be declined and that it be considered on an individual patient basis via the Named Patient Pharmaceutical Assessment (NPPA) policy.

5.3. The Committee **recommended** that tocilizumab should be funded for the management of grade 3 or 4 cytokine release syndrome associated with the administration of blinatumomab for the treatment of acute lymphoblastic leukaemia for patients being treated as part of the Children's Oncology Group (COG) AALL1331 trial.

5.4. The Committee **reiterated** its previous recommendation that PHARMAC review the mechanisms through which unfunded clinical trial treatments and associated supportive treatments, and paediatric oncology treatments, are reviewed and funded.

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

Discussion

5.6. The Committee noted that cytokine release syndrome (CRS) is a constellation of inflammatory symptoms resulting from cytokine elevations associated T cell engagement and proliferation, including interleukin-6, interleukin 10 and interferon-γ. Symptoms range from mild to severe with some patients experiencing severe inflammatory syndrome, including vascular leak, hypotension, pulmonary oedema and coagulopathy. Members noted this can result in multi-organ system failure and in some cases CRS-related death. Members noted that more profound CRS is related to a higher residual cancer burden and that while the application was for the more severe grade 3 and 4 CRS, patients with grade 2 CRS may also need to be admitted to intensive care units and require ventilation or other respiratory support and monitoring.

5.7. The Committee noted that CRS commonly occurs with chimeric antigen receptor modified T cell therapy (CART) and novel bispecific T-cell engaging (BiTE) single-chain antibody constructs that links CD3 T lymphocytes with CD19 B cells such as blinatumomab. Members also noted that there are rare reports of CRS associated with other biologic treatments including rituximab (anti-CD20), anti-thymocyte globulin (ATG), OKT3 (anti-CD3), TGN1412 (CD-28) and alemtuzumab (anti-CD52). Members noted that in future there would be more treatments available that could cause CRS.

5.8. The Committee noted that PHARMAC had also received and approved two Named Patient Pharmaceutical Assessment (NPPA) applications for tocilizumab for the treatment of CRS related to biologic treatments, one for blinatumomab compassionate supply and one for autologous T cell therapy to target Hepatitis B affected cancer cells.

5.9. The Committee noted the COG relapsed/refractory ALL AALL1331 trial uses a combination of standard care chemotherapy and immunotherapy in the form of blinatumomab. Members noted that there may be 1 to 2 children per year enrolled in this clinical trial that would be randomised to the arm with blinatumomab. It is expected that only 1 to3 doses of tocilizumab would be required to treat CRS if it occurred. Members noted that if blinatumomab cannot be safely administered the opportunity for these patients to participate in the COG trial would be lost.

5.10. Members noted that tocilizumab has become a standard rescue therapy for CRS within ongoing clinical trials due to its rapid, dramatic response and lack of apparent side effects. The goal of management is not to obliterate all CRS but to prevent life-threatening toxicity while maximising the potential for anti-tumour effects. The Committee noted that treatment of severe CRS with tocilizumab is associated with dramatic improvement in fever, tachycardia, and resolution of severe symptoms within minutes to hours. Cardiovascular dysfunction subsequently improves, with more protracted recovery for other organ dysfunctions.

5.11. The Committee noted a retrospective observational study by Fitzgerald et al. (Crit Care Med 2016; published online 25 September 2016) reported that 32 out of 39 children treated with CAR modified T cell therapy developed CRS, with 46% experiencing grade 3 – 4 CRS. Members noted 36% of patients were treated with vasoactive infusions for a median of 5 days after T cell therapy and 15% developed acute respiratory failure and required mechanical ventilation for a median period of six days. Thirteen patients that were treated with tocilizumab showed rapid improvement, with nine patients only requiring one dose. All patients with grade 4 CRS that received tocilizumab survived and achieved disease remission.

5.12. The Committee considered that overall there was limited evidence to support the use of tocilizumab in the treatment CRS. Members noted the evidence was limited to case reports but that these did present convincing evidence of rapid improvement. At this stage Committee recommended that tocilizumab should not be listed on Pharmaceutical Schedule for the treatment of grade 3 and 4 CRS and that requests for individual patients should continue to be assessed via NPPA. Members considered that widening access to tocilizumab for CRS should be considered when and if PTAC considers treatments that can cause CRS for listing on the Pharmaceutical Schedule.

5.13. Members noted blinatumomab is not currently available in New Zealand outside of the COG clinical trial. The Committee were supportive of paediatric patients who are enrolled in oncology clinical trials having access to treatments that are required in order to participate in these clinical trials. The Committee considered an HML exemption would be appropriate for all patients who are a part of the COG Refractory ALL – AALL1331 trial. The Committee further considered that PHARMAC should address the wider policy issue regarding paediatric patients in clinical trials and felt that these supporting treatments should be available.

6. Alglucosidase alfa-rch for late onset Pompe disease

Application

6.1. The Committee reviewed an application from Sanofi Genzyme for alglucosidase alfa (Myozyme) for the treatment of late onset Pompe disease (LOPD).

Recommendation

6.2. The Committee **recommended** that the application for alglucosidase alfa for the treatment of late onset Pompe disease be declined.

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

Discussion

6.4. The Committee noted that it had reviewed the evidence regarding the use of alglucosidase alfa for the long-term treatment of late-onset Pompe disease (LOPD) on a number of occasions between 2009 and 2014, but that this application was the first supplier-led application that had been submitted to the Committee for review. The Committee noted that PTAC had previously recommended alglucosidase alfa for LOPD be declined; the Committee had noted at that time the significant unmet health need faced by patients with Pompe disease, but had considered this to be outweighed by the lack of evidence for clinically significant benefit and the disproportionately high cost of a potentially disease-modifying treatment.

6.5. Members noted that key uncertainties previously raised by PTAC included the limited evidence to support long-term improvement in morbidity and mortality, variability in treatment response, response to treatment with regards to time from diagnosis and irreversibility of certain changes, suitability of measures to monitor treatment effect, uncertainty around infusion associated reactions and antibody formation, and overall relative poor cost effectiveness.

6.6. The Committee noted that Pompe disease is a rare lysosomal storage disease caused by a deficiency of lysosomal enzyme acid alfa-glucosidase (GAA), which results in accumulation glycogen in almost all tissues but predominantly skeletal muscle.

6.7. The Committee noted that there are two subtypes of Pompe disease: infantile-onset, which is diagnosed in the first year of life and causes serious disease including cardiomyopathy; and LOPD, where diagnosis is made at over one year of age or under one but without cardiomyopathy. Members noted LOPD can start as early as the first

decade of childhood, or as late as the sixth decade of adulthood and that juvenile-onset Pompe disease is a subset of LOPD.

6.8. Members noted that PHARMAC had recently consulted on a proposal, to list alglucosidase alfa for infantile-onset Pompe disease, subject to Special Authority criteria, resulting from the Medicines for Rare Disorders Request for Proposals that PHARMAC ran in 2014.

6.9. The Committee noted that LOPD is a multisystem disorder, with respiratory failure the most common cause of death. Members noted that disease progression can be highly variable and in general, the later the diagnosis, the better the prognosis. The reported median survival without enzyme replacement therapy (ERT) is 27 years, and patients may survive for decades following diagnosis. Therefore, it would be expected that patients would remain on ERT for many years. Members noted a study by Kanters et al. (J Inherit Metab Dis. 2011;34:1045-52) estimated the average quality of life utility for patients with LOPD was 0.72, compared to 0.87 in a representative sample population. Disease severity in the study was determined on the basis of the use of ambulatory and respiratory support.

6.10. The Committee noted the supplier had estimated the incidence at 1 in 14,000 to 1 in 300,000 people per year. There are currently only 10 confirmed patients with LOPD in New Zealand, with at least two of those patients identifying as Māori. The Committee noted that there is no funded ERT for LOPD currently available in New Zealand and patients are managed with supportive and symptomatic care. Members acknowledged the difficult position these patients and their clinicians are in.

6.11. The Committee noted that since its last review of alglucosidase alfa in 2011, a large amount of published information has become available and this had been referenced by the supplier in the application.

6.12. The Committee noted there remains only one randomised control trial (Van der Ploeg et al. NEJM 2010;362:1396-406) comparing alglucosidase alfa with best supportive care in patients with LOPD (the LOTS trial) and that this study had been considered by the Committee in 2011. Ninety patients were randomly assigned to receive alglucosidase alfa placebo for 78 weeks. The Committee again noted the results of the trial, in particular with regards to the improvements in six minute walk test (6MWT) and forced vital capacity (FVC). Members noted that in its previous reviews the Committee had compared the 6MWT results with those typically used for patients with Chronic Obstructive Pulmonary Disease (COPD) to demonstrate clinically significant improvements. In particular, members noted that Van der Pleog et al. (2010) reported a mean improvement of 28 metres (6MWT) with alglucosidase alfa compared with placebo (p=0.03), whereas trials of treatments for COPD typically use improvements of 50 metres or more to demonstrate clinical significance. The Committee noted the supplier's view that as patients with LOPD also suffer from skeletal muscle disease it is not appropriate to compare results with COPD patients, which is a respiratory disease only. Members noted there was an absolute increase of 3.4% in FVC in the alglucosidase alfa group compared with placebo (p=0.006). Regarding secondary and tertiary efficacy endpoints of pulmonary function and muscle quantitative muscle testing, a significant difference was only demonstrated in maximum expiratory pressure.

6.13. The Committee noted there was an open label extension study to the LOTS trial (Van der Ploeg et al. NEJM 2012;456-71)) that included 55 patients who received alglucosidase alfa for a further 26 weeks. The extension study took patients on active treatment in the initial 78 week double blinded LOTS study through to 104 and 130 weeks showing that there is no further improvement and a slight drift downward in 6MWT and FVC confirming that the improvement in 6MW and FVC occurred by week 26. Members noted the mean increase in distance walked for the 6MWT from LOTS

baseline to 104 weeks was 21.3 ± 78 m and the mean change in % predicted FVC was 0.8% ± 6.7% from baseline.

6.14. The Committee noted data from the 30 individuals that had been on placebo for the first 78 weeks who crossed over. 26 individuals went on to active therapy for 26 weeks with a further 13 continuing to 52 weeks. Members noted the results of this placebo crossover were inconsistent with the original LOTS results. There was only a 4.2 metre increase at 26 weeks in 6MWT (compared with a 3 metre increase in the 6MWT in the original 26 week placebo arm) and a decline of -1% in FVC at 26 weeks (compared with a decline of 0.4 in the original 26 week placebo arm). This data is in contrast to the 26 week data on the active arm in the first 26 weeks of LOTS trial where the 60 patients had a 25-30 metre increase in 6MW and a 1.5% increase in FVC. Data from the 13 patients that continued treatment for 52 weeks was not available.

6.15. Members also noted a post-hoc analysis of LOTS (Orlikowski et al. Neuromuscular Disorders 2011;21:639-751 – abstract only) comparing non-invasive ventilation needs in patients who received ERT versus placebo treated patients. No statistically significant differences were identified after 18 months treatment in patients using non-invasive ventilation at baseline.

6.16. The Committee noted 18 cohort studies from the Erasmus Group and Pompe Register and various other European countries. Members noted a prospective international observational study (Güngor et al. Orphanet J Rare Disease 2013;8:49) assessing the effect of treatment with ERT on survival that was considered by the Committee in 2014. Members reiterated that the Committee agreed that this study suggested alglucosidase alfa may offer benefit on overall survival, however, there is still a significant amount of uncertainty due to the methodology of the study. Many other cohort studies were noted by the Committee, including (but not limited to):

- Anderson et al. J Inherit Metab Dis. 2014;37(6):945-52.
- Boentert et al. Eur J Neurol. 2015;22(2):369-76, e27.
- de Vries et al. Neuromuscular Disorders. 2014;24(9-10):870.
- de Vries et al. Orphanet J Rare Disease. 2012;7:73-82.
- Güngor et al. J Inherit Metab Dis. 2016;39(2):253-60.
- Güngor et al. Mol Genet Metab. 2013;109(4):371-6.
- Güngor et al. Mol Genet Metab. 2013;109:174-8.
- Hundsberger et al. J Neurol. 2014;261(9):1684-90.
- Stepien et al. Mol Genet Metab. 2015;114(2):S111.
- Stepien et al. Mol Genet and Metab. 2016;117(4):413-8.
- Van der Ploeg et al. Mol Genet Metab. 2015;114(2):S121.
- Wyatt et al. Health technology assessment (Winchester, England). 2012;16(39):1-543.

6.17. The Committee reviewed a meta-analysis by Kanters et al. (Redwood Outcomes report, unpublished academic-in-confidence) [now published] which examined the associations between ERT treatment and survival, progression of muscle endurance, progression of pulmonary function and assessed the effect of treatment on wheelchair use and ventilator status (although it did not draw any conclusions regarding wheelchair use and ventilator status). The study used a variety of synthesis methods to evaluate 22 publications pertaining to 19 studies (438 patients) on the effect of treatment of LOPD with alglucosidase alfa. The Committee noted that only one comparative study was included in the analysis and that the rest were single arm studies of patients treated with alglucosidase alfa. The Committee also noted that the meta-analysis methods differed according to outcome type, the availability of comparative evidence and the availability of data pertaining to the prognostic factors.

6.18. The Committee noted that the analysis included 47 deaths, 28/79 (35%) in untreated patients and 19/302 (6.3%) in treated patients. The Committee noted that this resulted

in a rate ratio of 0.21 (95% CI 0.11-0.41), however, it also noted that one reported death event (in the study by Angelini et al. J Neurol. 2012;259:952-8.) had a large effect on the estimate of the rate ratio, appearing to halve the ratio, and that most of the mortality data was from one study (Güngor et al. Orphanet J Rare Disease 2013;8:49, discussed above). The potential for considerable confounding had been noted within the Güngor paper by PTAC in 2014.

6.19. The Committee noted that the 6MWT was reported in eight studies and included 201 patients, 171 of which received alglucosidase alfa. The Committee noted the average improvement in 6MWT with treatment was 43 metres after 12 months and 59 metres over three years. It noted that the largest improvement was over the first 20 months of treatment and that untreated patients remained stable.

6.20. The Committee noted that Forced Vital Capacity (FVC) was reported in 11 studies (including one comparative study and two single arm studies with untreated patients) and included 451 patients, 298 of which received treatment with alglucosidase alfa. The Committee noted that in untreated patients, FVC %-predicted consistently decreased by 2.3% after 12 months and 6.2% after four years. Whereas in patients that received treatment, FVC %-predicted initially improved 1.4% after two months, then gradually returned to baseline after three years. It also noted that the relative differences in FVC increases from 4.5% after 12 months and reaches 6% at four years.

6.21. The Committee noted a systematic review by Schoser (BMC Musculoskeletal Disorders 2013;14(S2):O9) which was presented as a summary of a verbal presentation. Members noted that it evaluated the clinical efficacy and safety of alglucosidase alfa treatment in juvenile and adult patients with LOPD across 22 studies (437 patients). The Committee noted that no statistical analysis had been performed due to data heterogeneity. The review concluded that creatine kinase (CK) levels stabilised or improved in at least two thirds of patients, and that other measures of muscular and/or respiratory function improved following treatment. It was also reported that alglucosidase alfa was well tolerated, with the majority of adverse events were mild or moderate infusion-related reactions. The Committee noted the author commented that further research is required to investigate reliable prognostic factors (age at start of ERT, phenotypic presentation, genotypic characteristics) to enable better management of LOPD patients.

6.22. The Committee noted another systematic review by Toscano and Schoser (J Neurology 2013;260(4):951-9) that also evaluated the efficacy and safety of alglucosidase alfa treatment in juvenile and adult patients with LOPD, across 21 studies (368 patients), but also included no statistical analysis. The Committee noted that over all the findings were similar to that reported by Schoser. CK levels decreased in around 70% of patients, stabilised in around 11% and increased in around 19%. With regards to 6MWT results, data was available for 122 patients from seven studies, 77.9% improved, 8.2% stabilised and 13.9% declined. Mean improvement ranged from 10 to149 metres. The Committee noted that ambulatory status was not taken into account in most studies. In untreated LOPD, the probability of wheelchair use increases on average 13% each year of diagnosis. Impaired baseline ambulatory status was reported in 115 patients and 7 patients experienced an improvement following treatment. One study reported a patient who was wheelchair-bound prior to treatment walked without assistance after 72 weeks following weekly ERT. The Committee noted that most patients improved as treatment continued after the first year. Analysed data showed no clear association between longer duration of treatment and further motor function improvements. Those patients who declined in the first 12 - 23 months of treatment did not improve with longer duration of ERT. Members noted only 13 out of 176 patients reported an improvement in quality of life following treatment.

6.23. The Committee considered that evidence regarding alglucosidase alfa for LOPD

remains weak, of moderate quality, is largely non-experimental, and the pooled data from non-experimental studies may be subject to bias in estimates of effects favouring the treatment. Members noted that alglucosidase alfa may be beneficial for a few individuals who could potentially experience clinical improvement with ERT, but considered however that it is extremely difficult to determine for which patients this could be the case from currently available clinical data. The Committee considered the clinical benefits with regards to ambulation and pulmonary function are modest and the survival benefit remains uncertain.

6.24. The Committee noted that the variable uptake of alglucosidase alfa into cells and the development of antibodies both limit the effectiveness of this treatment. Members noted that a new ERT is in development (neoGAA) in Phase III trials that may improve intracellular drug activity. Members noted that they look forward to seeing the results of this trial in the future.

6.25. Members also noted a recent trial BMN701 (Phase III INSPIRE trial) from another supplier was recently discontinued worldwide and is no longer being developed. Members noted that three New Zealanders had been participating in this trial and now have no alternative treatment.

6.26. The Committee considered that despite the significant price reduction included in the proposal, the treatment remains extremely expensive and poorly cost effective. Members noted that the cost-utility analysis modelling had been updated to include the reduced price, and although there was some resultant improvement in cost-effectiveness, the results remained at less than [redacted] despite very optimistic assumptions. The Committee noted that although the new information had been presented in the submission and the Committee had carefully reviewed this, the view of the Committee regarding previous uncertainties regarding alglucosidase alfa for LOPD remain unchanged.

7. Pembrolizumab for locally advanced, or metastatic, unresectable, PD-L1 positive, non-small cell lung cancer

Application

7.1. The Committee considered an application from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab (Keytruda) as monotherapy for the second or third-line treatment of locally advanced, or metastatic, unresectable, non-small cell lung cancer (NSCLC) expressing PD-L1 at a level of equal or greater than 1%.

Recommendation

7.2. The Committee **recommended** that pembrolizumab as monotherapy be funded with low priority for the second or third-line treatment of locally advanced, or metastatic, unresectable NSCLC expressing PD-L1 at a level of equal or greater than 1%.

7.3. The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for advice regarding the appropriate duration of treatment, utility of PD-L1 as a biomarker, and development of Special Authority criteria.

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

Discussion

7.5. The Committee noted that pembrolizumab is a humanized IgG4 monoclonal antibody PD-1 inhibitor indicated (1) for the treatment of advanced melanoma, (2) for the treatment of patients with advanced NSCLC whose tumours express PD-L1 and who have received platinum-containing chemotherapy. The Committee also noted that the registered NSCLC indication included that any patients with EGFR or ALK genomic

tumour aberrations should already have received approved therapy for these aberrations prior to receiving pembrolizumab.

7.6. The Committee noted that funding for another PD-1 inhibitor, nivolumab (Opdivo, Bristol Myers-Squibb), as monotherapy for the treatment of locally advanced or metastatic squamous and non-squamous NSCLC in second/third-line settings for patients who have progressed on or after prior platinum based chemotherapy, was considered by the Cancer Treatments Subcommittee of PTAC (CaTSoP) at its meeting in April 2016 and PTAC in May 2016.

7.7. The Committee noted that CaTSoP had recommended that nivolumab as monotherapy be funded for these patient populations with medium/low priority, and also that CaTSoP had recommended that nivolumab be funded for patients with EGFR mutation positive locally advanced or metastatic nonsquamous NSCLC that has progressed after both prior platinum-based chemotherapy and erlotinib or gefitinib with medium/low priority. The Committee noted that PTAC had recommended nivolumab as monotherapy be funded for these three patient populations with a low priority, taking into account the high health need of the patient populations but also noting the immaturity of the data, the limited and uncertain incremental benefit over current treatments, and the high price sought by the supplier.

7.8. The Committee noted that approximately 2000 people are registered with a diagnosis of lung cancer in New Zealand each year, and it was the leading cause of cancer death accounting for 19% of all cancer deaths. The Committee noted that survival rates for patients with advanced disease are poor with current treatments.

7.9. The Committee noted that registration and mortality rates for lung cancer are consistently higher for Māori than for non-Māori with incidence and mortality 2-3 times higher in Māori males and 3-4 times higher in Māori females, compared with non-Māori.

Evidence

7.10. The Committee noted the key evidence for the use of pembrolizumab for the treatment of PD-L1 positive NSCLC comes from KEYNOTE-010 (Herbst et al. Lancet 2016;387:1540-50), a randomised, open-label, phase 2/3 study of pembrolizumab compared with docetaxel in 1034 patients with previously treated, PD-L1 positive (PD-L1 expression >1%), advanced NSCLC.

7.11. The Committee noted that patients were randomly assigned 1:1:1 to receive pembrolizumab at a dose of 2 mg/kg every 3 weeks (n=345) or 10 mg/kg every 3 weeks (n=346) or docetaxel (75 mg/kg every 3 weeks, n=343) for 24 months or until confirmed disease progression, intolerable toxic effects, physician decision, patient withdrawal or other reasons. The Committee noted that patients who progressed according to investigator-assessed immune-related response criteria (irRC) could remain on treatment until a confirmatory scan was undertaken 4-6 weeks later. The Committee noted that patients in the docetaxel arm were not permitted to cross over to receive pembrolizumab.

7.12. The Committee noted that eligibility criteria included measurable disease and progression as per RECIST version 1.1, ECOG performance status of 0 or 1, and PD-L1 expression on at least 1% of tumour cells (ie a tumour proportion score of ≥1%). The Committee noted that patients were stratified by extent of PD-L1 expression (tumour proportion score (TPS): strong ≥50% vs. weak 1-49%).

7.13. The Committee noted that the initial trial design permitted any tumour sample for PD-L1 testing, but the study protocol was later amended to require a new tumour sample for PD-L1 testing except when attempting to take a biopsy would be too risky. The

Committee noted that to be considered a new sample that no intervening treatment was permitted between the time the sample was taken and initiation of study treatment; with the exception for patients receiving tyrosine kinase inhibitors before the biopsy was taken who were permitted to resume them after sample collection.

7.14. The Committee noted that exclusion criteria included previous treatment with PD-1 inhibitors or docetaxel, active brain metastases, interstitial lung disease requiring systemic corticosteroids, or a history of pneumonitis requiring systemic corticosteroids.

7.15. The Committee noted that at a median follow-up of 13.1 months (IQR 8.6-17.7), 521 patients had died: 172 (50%) of 344 in the pembrolizumab 2 mg/kg group, 156 (45%) of 346 in the pembrolizumab 10 mg/kg group, and 193 (56%) of 343 in the docetaxel group.

7.16. The Committee noted that after discontinuation of study treatment, additional antineoplastic treatment was received by 138 (40%) of 344 patients in the pembrolizumab 2 mg/kg group, 133 (38%) of 346 patients in the pembrolizumab 10 mg/kg group, and 151 (44%) of 343 patients in the docetaxel group, including two (1%), six (2%), and 45 (13%), respectively, who received other immunotherapies.

7.17. The Committee noted that in the total population, the hazard ratio (HR) for overall survival (OS) for pembrolizumab 2 mg/kg versus docetaxel was reported as 0·71 (95% CI 0·58–0·88; p=<0.01) and the HR for pembrolizumab 10 mg/kg versus docetaxel was 0·61 (0·49–0·75; p<0·01) and median OS was 10·4 months (95% CI 9·4–11·9) for the pembrolizumab 2 mg/kg group, 12·7 months (10·0–17·3) for the pembrolizumab 10 mg/kg group, and 8·5 months (95% CI 7·5–9·8) for the docetaxel group.

7.18. The Committee noted that in patients with a PD-L1 tumour proportion score of 50% or greater, the HR for overall survival for pembrolizumab 2 mg/kg versus docetaxel was 0·54 (95% CI 0·38–0·77; p=0·0002), and for pembrolizumab 10 mg/kg versus docetaxel it was 0·50 (0·36–0·70; p<0·0001). The Committee noted that median overall survival was 14·9 months (95% CI 10·4–not reached) for the pembrolizumab 2 mg/kg group, 17·3 months (11·8–not reached) for the pembrolizumab 10 mg/kg group, and 8·2 months (6·4–10·7) for the docetaxel group.

7.19. The Committee considered OS to be very similar between the two pembrolizumab groups, both in patients with a PD-L1 tumour proportion score of 50% or greater (HR for 2 mg/kg vs 10 mg/kg 1·12, 95% CI 0·77–1·62) and in the total study population (1·17, 0·94–1·45).

7.20. The Committee noted that progression-free survival was longer with pembrolizumab than with docetaxel in patients with a tumour proportion score of 50% or greater, with an HR of 0·59 (95% CI 0·44–0·78; p<0·01) for pembrolizumab 2 mg/kg versus doxetaxel and 0·59 (0·45–0·78; p<0·01) for pembrolizumab 10 mg/kg versus docetaxel.

7.21. The Committee noted that the median duration of treatment was 3·5 months (IQR 1·4–7·2) in the pembrolizumab 2 mg/kg group, 3·5 months (1·4–7·0) in the pembrolizumab 10 mg/kg group, and 2·0 months (0·8–3·6) in the docetaxel group.

7.22. The Committee noted that grade 3–5 adverse events attributed to study treatment occurred in 43 (13%) of 339 patients in the pembrolizumab 2 mg/kg group, 55 (16%) of 343 patients in the pembrolizumab 10 mg/kg group, and 109 (35%) of 309 patients in the docetaxel group, and deaths attributed to study treatment occurred in three patients in the pembrolizumab 2 mg/kg group (two cases of pneumonitis and one of pneumonia), three patients in the pembrolizumab 10 mg/kg group (one case each of myocardial infarction, pneumonia, and pneumonitis), and five patients in the docetaxel group (one case each of acute cardiac failure, dehydration, febrile neutropenia,

interstitial lung disease, and respiratory tract infection).

7.23. The Committee noted updated results from KEYNOTE010 presented at ESMO 2016, reporting after a median follow up of 19.2 months, where 18 month OS rates for TPS ≥1% were 37% in the 2mg/kg arm, 43% in the 10mg/kg arm and 24% in the docetaxel arm; and the TPS ≥50% corresponding 18 month OS rates were 46%, 52%, 24% respectively.

General comments

7.24. The Committee noted that the Medsafe datasheet states patients should be selected for treatment of advanced NSCLC with pembrolizumab based on the presence of positive PD-L1 expression and that determination of PD-L1 expression should be performed using a validated test by laboratories with demonstrated proficiency in the in-vitro diagnostic technique being employed.

7.25. The Committee also noted that in Garon et al. (NEJM 2015;372:2018-28), which evaluated data from the advanced NSCLC arm of the phase 1 KEYNOTE001, the authors had concluded 'tumor PD-L1 expression is not associated with the ideal test characteristics of approved genetically based biomarkers' and 'PD-L1 expression could be affected by previous treatment or by disease stage'. The Committee further noted that Garon et al. had considered that while responses observed in patients not predicted by PD-L1 staining could result from tumour heterogeneity, the authors considered it more likely that tumor PD-L1 expression alone does not accurately assess the dynamic immune microenvironment.

7.26. The Committee considered the chosen PD-L1 expression stratification levels in KEYNOTE010 appeared to be essentially arbitrary and that it was likely patients with PD-L1 expression of below 1% could benefit from treatment with pembrolizumab.

7.27. The Committee noted that PD-L1 expression testing was not currently available in New Zealand, and considered there would be costs associated with establishing and maintaining the required testing facilities and training staff.

7.28. The Committee considered there was significant uncertainty regarding the optimal duration of treatment for patients with advanced NSCLC, and longer term survival data was needed. The Committee noted that the KEYNOTE010 trial protocol capped treatment duration at 24 months.

7.29. The Committee noted that no data had been provided by the applicant regarding the prevalence of PD-L1 expression in the New Zealand population and considered there was uncertainty regarding the relevance of the trial data in a New Zealand setting.

7.30. The Committee noted that there was a lack of literature provided in the application regarding health-related quality of life for patients with advanced NSCLC or their families or whanau, and that further robust data was needed.

7.31. The Committee considered that, while pembrolizumab appears to represent an improvement in the treatment of advanced NSCLC over docetaxel, due to the significant immaturity of currently available data it was not clear if the observed trial-based improvements translate to long-term clinically meaningful overall survival gains.

7.32. The Committee considered that the evidence for the use of pembrolizumab is still developing and there is uncertainty regarding longer-term potential benefits and risks and how long the treatment should be used for. The Committee considered these uncertainties along with the high price being sought by the supplier was adversely affecting the cost-effectiveness of pembrolizumab.

7.33. The Committee noted that the National Institute for Health and Care Excellence NICE)

in the UK is consulting on whether to 'not recommend' pembrolizumab, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer in adults whose tumours express PD-L1 and who have had at least one prior chemotherapy regimen (and targeted treatment if they have an epidermal growth factor receptor- or anaplastic lymphoma kinase-positive tumour).

7.34. The Committee noted that trials were currently being undertaken into the use of pembrolizumab in the first-line advanced NSCLC setting and that an application for this was expected from the supplier in early 2017.

8. Widened access to temozolomide for high grade gliomas

Application

8.1. The Committee considered an application from a clinician for widened access to temozolomide for the following indications:

- newly diagnosed high grade glioma (grade III and IV), without concomitant radiation, for patients who are older than 60 years and/or have poor performance status (KPS<70); and
- relapsed/recurrent high grade glioma (grade III and IV).

Recommendation

8.2. The Committee **recommended** that the application for temozolomide for patients with newly diagnosed high grade glioma (grade III and IV), without concomitant radiation, for patients who are older than 60 years of age and/or have a poor performance status (Karnofsky performance status (KPS)<70) be declined.

8.3. The Committee **recommended** that the application for temozolomide for relapsed/recurrent high grade glioma (grade III and IV) without concomitant radiotherapy should be declined.

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

Discussion

8.5. The Committee noted that gliomas account for over 80 percent of primary brain malignancies and that approximately 160 patients are diagnosed with high grade gliomas (grade III anaplastic astrocytoma or grade IV glioblastoma mulitforme) each year in New Zealand.

8.6. The Committee noted that high grade primary brain cancers are not curable and treatment is aimed at reducing symptoms and prolonging disease free progression and survival times. The Committee noted that patients with glioblastoma multiforme have a median survival of approximately 9 months with a 5-year survival rate of less than 5%, while anaplastic astrocytomas have a better, but still poor prognosis, with average survival of 2-5 years.

8.7. The Committee noted that current treatment for high grade gliomas include debulking surgery and, where possible, combined with adjuvant radiotherapy and chemotherapy treatment. The Committee noted that there appeared to be no standard treatment regimen for relapsed disease.

8.8. The Committee noted that temozolomide is currently funded for patients with newly diagnosed high grade gliomas administered concomitantly with radiotherapy at a maximum dose of 200 mg/m^2 per day for 5 days per treatment cycle.

8.9. The Committee noted that temozolomide is indicated for the treatment of newly

diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment, and recurrent high grade glioma. The Committee noted that temozolomide is not registered by Medsafe for the treatment of patients with newly diagnosed high grade gliomas without radiotherapy.

8.10. The Committee noted that the Cancer Council Australia and the National Institute for Health Care Excellence (NICE) in the UK recommend that temozolomide should only be administered to patients with good performance status or KPS score of ≥70; and that temozolomide is listed on the Pharmaceutical Benefits Schedule (PBS) in Australia restricted to patients undergoing concomitant radiotherapy.

Newly diagnosed high grade gliomas, without concomitant radiation, >60 years old or poor performance status

8.11. The Committee reviewed evidence for the use of temozolomide without radiation for the treatment of newly diagnosed high grade gliomas for patients over 60 years of age and/or with KPS <70 including three Phase III studies:

- Wick et al Lancet Oncol 2012; 13:707-15 - a phase 3 randomised controlled non-inferiority trial comparing the 100mg/m2 temozolomide alone versus 60/30 radiotherapy in 373 elderly patients with anaplastic astrocytoma or glioblastoma. The Committee noted that the patient population in this trial differed to the requested patient group as participants had KPS scores greater than 60. They noted that the dosage regime in the trial was also lower than that requested, (100mg/m2 temozolomide, given on days 1-7 of week on, 1 week off cycles). The Committee noted that median overall survival (OS), the primary endpoint of the study, was 8.6 months and 9.6 months in the temozolomide and radiotherapy arms respectively. The Committee noted that Grade 2-4 serious adverse events were more frequent in the temozolomide group than the radiotherapy group but considered that quality of life scores appeared similar in both groups.
- Malström et al. Lancet Oncol 2012; 13:916-26 - a phase 3 randomised controlled trial comparing 200mg/m2 temozolomide with hypofractionated radiotherapy (34Gy) or standard radiotherapy (60Gy) in 342 patients 60 years or older with newly diagnosed glioblastoma and WHO performance status 0-2. The Committee considered that this patient population differed to the requested population which would be equivalent to WHO performance status of 2 or higher and a KPS >70 The Committee noted that OS was 8.4 months for the temozolomide arm compared to 7.4 months in the 34Gy radiotherapy arm and 6.0 months in the 60Gy radiotherapy arm. The Committee noted that 34% of the temozolomide group received salvage radiotherapy and 41% received a second line treatment which complicated interpretation of the trial results.
- Perry et al J Clin Oncol 34, 2016, suppl; abstr LBA2 - a phase 3 randomised controlled trial comparing 40 Gy radiotherapy with 40 Gy radiotherapy and adjuvant temozolomide until progression or 12 cycles in 562 patients over 65 years of age with newly diagnosed glioblastoma and ECOG status 0-2. The Committee considered that the patient population in this study differed to the requested population which would correlate to an ECOG status of 2 or greater. The Committee also noted that the continuous low dose-intense regime was different from that proposed (50 mg/m2/d for up to 1 year or until progression occurred). The Committee noted that median OS was 9.3 months in the temozolomide arm compared with 7.6 months in the radiotherapy arm and that MGMT methylated patients (n=462) were reported to benefit more than MGMT unmethylated patients (OS 13.5 months vs 7.7 compared to 10.0 vs 7.9 in the temozolomide and radiotherapy arms respectively).

8.12. The Committee also noted evidence for the use of temozolomide from a number of small retrospective or observational studies and case series including but not limited

to:

- Glantz et al. Cancer 2003; 97:2262-6
- Chinot et al. Cancer 2004; 100:2208-14
- Perez-Larray J Clin Oncol; 2012; 29:3050-55
- Minniti et al. Int J Radiat Oncol Biol Phys; 2012; 1;83:93-9:
- Minniti et al. J Neurooncol; 2008; 88:97-103

8.13. The Committee considered evidence for the use of temozolomide without radiation for the treatment of patients over 65 years or with poor performance status to be of reasonable strength but low quality being generally from studies for different population groups to those requested.

Relapsed high grade gliomas

8.14. The Committee reviewed evidence for the use of temozolomide for the treatment of relapsed/recurrent high grade glioma including, but not limited to the following::

- Yung et al. Br J Cancer 2000; 83:588-593
- Brada et al J Clin Oncol 2010; 28:4601-08
- Filipinni et al. Neurooncl 2008; 79-87
- Brandes et al. Br J Cancer 2006; 95:1155-60
- Oshoba J Clin Oncol 2000; 83:588-593
- Sijben et al.J Neurooncl; 2008; 89: 97-103

8.15. The Committee considered the evidence for the use of temozolomide for the treatment of relapsed high grade gliomas to be of low strength and poor quality and that the appropriate comparator treatment was unclear. The Committee also considered that the optimal dose regimen for temozolomide in the treatment of relapsed high grade gliomas was uncertain.

General comments

8.16. The Committee noted a literature review of the clinical data on the use of temozolomide in elderly patients with GBM (Chagari et al Cancer Treatment Reviews 2012;38:988-95) and that the authors concluded that 'no study has prospectively demonstrated a benefit of radiotherapy, chemotherapy or both in patients more than 70 years old with additional poor prognostic factors e.g. KPS<70'.

8.17. The Committee considered it was uncertain whether temozolomide would provide any additional benefit in the requested patient population when compared to radiotherapy alone. The Committee noted that Keime-Guibert et al. (N Engl J Med; 2007:356:1527-35) concludes that radiotherapy results in modest improvement in survival, without reducing the quality of life or cognition, in elderly patients with glioblastoma.

8.18. The Committee considered that there may be a quality of life benefit for patients outside main centres receiving treatment with temozolomide without radiotherapy in terms of reducing the need to travel or relocate for a period of time, however, the Committee noted no evidence was provided to support this.

8.19. The Committee noted most studies state that temozolomide is well tolerated, however, grade 3 or 4 serious adverse events occur in up to 25% of patients treated with temozolomide and may be more common in elderly patients; for example Sijben et al. (ibid.) report grade 3 or 4 serious adverse events in 42% of elderly patients (n=39).

8.20. The Committee considered that MGMT promoter methylation may predict patients

most likely to respond to treatment with temozolomide, however, further evidence was needed regarding its reliability as a biomarker.

8.21. The Committee considered that overall there was a lack of evidence for the use of temozolomide in the requested patient groups and, based on the evidence currently available, it was highly uncertain what level of benefit, if any, these patients may derive from treatment with temozolomide as requested.

8.22. The Committee noted that there were a large number of ongoing trials currently investigating the use of temozolomide for the treatment of high grade gliomas.

9. Widened access to somatropin for Prader-Willi Syndrome – patients under the age of two years and adults

Application

9.1. The Committee considered a submission from the Prader-Willi Syndrome Association for the funding of somatropin in patients with Prader-Willi Syndrome (PWS); specifically, with regards to patients under the age of two years and adults and adolescents with PWS.

Recommendation

9.2. The Committee recommended that the initial Special Authority criteria for somatropin be widened to include treatment of patients with PWS over the age of six months as follows (additions in bold, deletions in strikethrough), with no changes to the current renewal criteria, with a medium priority:

Initial application — (Prader-Willi syndrome) only from a paediatric endocrinologist or endocrinologist. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:
1 The patient has a diagnosis of Prader-Willi syndrome that has been confirmed by genetic testing or clinical scoring criteria; and
~~2 The patient's height velocity is < 25th percentile (adjusted for bone age/pubertal status if appropriate) as calculated over 6 to 12 months using the standards of Tanner and Davies (1985); and~~
~~3 Either:~~
~~3.1 The patient is under two years of age and height velocity has been assessed over a minimum six month period from the age of 12 months, with at least three supine length measurements over this period demonstrating clear and consistent evidence of linear growth failure (with height velocity < 25th percentile); or~~
~~3.2 The patient is aged two years or older; and~~
2 The patient is aged six months or older; and
3 A current bone age is < 14 years (female patients) or < 16 years (male patients); and
4 Sleep studies or overnight oximetry have been performed and there is no obstructive sleep disorder requiring treatment, or if an obstructive sleep disorder is found, it has been adequately treated under the care of a paediatric respiratory physician and/or ENT surgeon; and
5 Either:
5.1 Both:
5.1.1 The patient is aged two years or older; and
5.1.2 There is no evidence of type II diabetes or uncontrolled obesity defined by BMI that has increased by ≥ 0.5 standard deviations in the preceding 12 months; **or**
5.2 The patient is aged between six months and two years and thorough ~~ENT assessment for airway obstruction~~ upper airway assessment is planned to be undertaken prior to treatment commencement and at six to 12 weeks following treatment initiation.

9.3. The Committee recommended that the application to widen access to somatropin to include treatment of adults and adolescents with PWS with skeletal maturity as defined by a bone age >14 years (female patients) or >16 years (male patients) be declined.

9.4. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for this recommendation.

Discussion

9.5. The Committee noted that PWS is a rare genetic disorder affecting three to four new

patients per year in New Zealand and is characterised by severe muscular hypotonia in the neonatal period resulting in feeding difficulties, mild to moderate intellectual disability, compulsivity, irritability, aggression, short stature, sleep apnoea and resulting cardio-respiratory problems, and eating disorders that include food cravings with extreme food-seeking behaviours that can lead to obesity.

9.6. The Committee noted that somatropin is currently funded for children with PWS subject to Special Authority criteria being met, which include the requirement for a minimum of 6 months of height velocity assessments from the age of 12 months.

9.7. The Committee noted that the applicant considers the primary benefit of somatropin for children with PWS is from changes in body composition, motor and cognitive development rather than improvement in linear height but that somatropin treatment is beneficial both when continued into adulthood and when started younger than the current access criteria allow.

9.8. The Committee noted the Endocrinology Subcommittee of PTAC considered widening of access to somatropin for PWS for children under the age of 2 years and adults at its meeting in June 2016 and had recommended that the initial Special Authority criteria for somatropin be widened to include treatment of patients with PWS over the age of six months with medium priority, and had recommended that funding of somatropin for adults and adolescents with PWS be declined due to a lack of evidence for clinically meaningful long term-benefit.

9.9. The Committee noted that somatropin is Medsafe registered for the treatment of patients with PWS: in children for the improvement of growth and body composition and in adults for the improvement of body composition.

9.10. The Committee noted that in 2008 the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia recommended somatropin for the improvement of body composition and short stature associated with PWS in patients up to 18 years of age. The Committee noted that in 2010, the National Institute for Health Care Excellence (NICE) in the UK recommended somatropin for growth failure associated with PWS where treatment is discontinued upon final height being obtained but that 'evaluation of response to therapy should also consider body composition'.

Patients under the age of two years and adolescents

9.11. The Committee noted Endocrinology Subcommittee's view that PWS patients are generally growth hormone deficient but variable growth velocity and that most patients with PWS would meet the current Special Authority criteria for somatropin at some point. Although it is possible that some PWS patients may not meet the current growth related access criteria.

9.12. The Committee noted a retrospective comparative cohort study from Australia in PWS children who received somatropin on the basis of short stature or evidence of growth hormone deficiency, compared with those treated based on a genetic diagnosis, indicated that patients in the genetic diagnosis cohort were likely to reach normal height but those in the growth hormone deficient cohort may not. (Scheermeyer J Paeds Child Health 2013;49:1045-51).

9.13. The Committee noted evidence for the use of somatropin in patients with PWS under the age of 2 years from a number of studies including two small, unblinded randomised controlled trials and three small non-experimental studies:

- Festen et al. Clin Endocrinol 2008;68:919-25
- Carrel et al. J Pediatrics 2004;145:744-9 (and updated results published as Whitman et al. J Paed Endo Met 2004;17:591-600, and Myers et al. Am J Med Genetics 2007;143A:443-8)

- Dykens et al. J Child Psychol Psychiatry 2016;doi10.1111/jcpp.12601
- Carrel et al. J Clin Endo Met 2010;95:1131-6
- Nyunt et al. J Paed Endo Met 2009;22:1151-8

9.14. The Committee considered that overall the currently available evidence for initiating treatment with growth hormone in patients under the age of 2 years was weak, being of low quality and low to moderate strength.

9.15. The Committee noted a systematic review of the clinical evidence in children and consensus guideline statement using 43 international experts (Deal et al. J Clin Endo Met 2013;98:1072-87), which stated that 'published data support benefits of growth hormone treatment when started between 4 and 6 months of age, but some experts are currently treating from as early as 3 months'.

9.16. The Committee considered that there is no consensus on the age at which somatropin treatment should start. The Committee considered that published reports indicate there appear to be short-term benefits in starting somatropin treatment before the onset of obesity, which often begins by 2 years of age.

9.17. The Committee noted the Endocrinology Subcommittee was not supportive of somatropin use in patients with PWS below the age of six months due to the lack of evidence and potential risks. The Committee agreed with the Subcommittee's view. The Committee noted that there are concerns regarding the effects of somatropin in stimulating tonsillar lymphoid tissue growth and therefore a significant greater risk of apneoa associated with airway obstruction with the treatment of younger infants.

9.18. The Committee considered that the access criteria recommended by the Endocrinology Subcommittee were broadly acceptable.

9.19. The Committee considered that there is a lack of long-term studies demonstrating the benefit of additional years of treatment beyond final height and that environmental factors, such as control of appetite by carers, are likely to have the largest impact on body composition changes. The Committee considered that the height velocity requirements in the renewal criteria were a surrogate for both the benefit effect of treatment and adherence to treatment and it was not appropriate they be removed.

9.20. The Committee considered that while it was a reasonable assumption, there is a lack of literature to support the view that earlier treatment with somatropin for patients with PWS may result in incremental changes to cognitive function and therefore leads to significant improvements in behaviour.

Adults

9.21. The Committee noted published evidence for use of somatropin in adults with PWS from a number of studies including four small randomized controlled trials and six small non-experimental studies:

- Sode-Carlsen et al. Endocrine 2012; 41:191-9
- Sode-Carlsen et al. GH & IGF Research 2011;24:185-90
- Kuppens et al. J Clin Endo Met 2016;101:4110-6
- Hoybbye et al. GH & IGF Research 2004;14:1-15
- Oto et al. Am J Med Genetics 2014;164A:671-5
- Mogul et al. J Clin Endo Met 2008;93:1238-45
- Gondoni et al. J Endo Invest 2008;31:765-72
- Bertella et al. J Intellectual Disability Research 2007;51:302-11

- Butler et al. GH & IGF Research 2013;23:81-7
- Lafortuna et al. J Clin Endo Met 2010;99:1816-24

9.22. The Committee considered that from the currently available published evidence it was unclear what benefit, if any, somatropin treatment provided for adult and adolescent patients with PWS. The Committee also considered it was uncertain if any long-term clinically meaningful benefit would be derived from somatropin treatment in this patient population.

10. Tiotropium bromide for treatment of severe asthma

Application

10.1. The Committee considered a submission from Boehringer Ingelheim for a Special Authority listing for the 'soft mist' form of tiotropium (Spiriva Respimat) on the Pharmaceutical Schedule for the treatment of severe asthma in adults who have experienced at least one exacerbation in the previous 12 months while receiving asthma therapy with at least an inhaled corticosteroid (ICS) and a long acting beta-2agonist (LABA).

Recommendation

10.2. The Committee recommended the application 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 the soft mist form of tiotropium (Spiriva Respimat) is listed on the Pharmaceutical Schedule for the treatment of chronic obstructive pulmonary disease (COPD) under Special Authority criteria that restrict use to patients with a FEV1 of below 60% of predicted and at Grade 3 or 4 of the Medical Research Council UK dyspnoea scale.

10.5. The Committee note that poor asthma control is multifactorial and includes factors such as overcrowding, poor housing, exposure to tobacco smoke, lack of spacer use with MDI inhalers, poor health literacy and other factors. The Committee noted that respiratory hospitalisation rates are higher for Pacific people and Māori (2.6 and 2.1 respectively) and that while deaths are uncommon, and largely preventable, Māori are four times more likely to die from asthma than non-Māori.

10.6. The Committee reviewed the two clinical trials, being twin phase III randomised double-blind placebo-controlled trials conducted concurrently over 48 weeks with identical study protocols and identical eligibility criteria, on which the submission was based (Kerstjens et al. N Engl J Med 2012;367:1198-207). The Committee noted that the trials comprised 912 adults with poor asthma control despite treatment with at least 800 micrograms (mcg) of budesonide or equivalent and a LABA, an Asthma Control Questionnaire (ACQ) 7 score of 1.5 or higher, and who had had at least one asthma exacerbation requiring oral corticosteroids in the previous 12 months, who were then randomised to tiotropium 5 mcg daily (2 puffs delivered by the Respimat) or placebo.

10.7. The Committee noted that people who were diagnosed with COPD and people who had recently smoked were excluded from the trials, and participants were required to have a post- bronchodilator FEV1 <80% and 70% FVC. The primary endpoints were peak and trough FEV1 at 24 weeks and the time to the first severe exacerbation requiring initiating or doubling of oral corticosteroids for at least 3 days measured over 48 weeks.

10.8. The Committee noted that after 24 weeks, tiotropium was reported to increase peak FEV1 compared with placebo with a mean difference of 86 ml +/-31 ml (95% confidence interval (CI) 20-152, p=0.01) in trial 1 and 154 ml +/-32 ml in trial 2 (95% CI 91-217, p=0.001) in trial 2. Pooled data from both studies across 48 weeks reported the time to first exacerbation increased in the tiotropium group from 226 days in the placebo group to 282 days ([hazard ratio (HR)] 0.79, 95% CI 0.65-1.00, p=0.003). The Committee noted that 122/453 people (26.9%) in the tiotropium group had an exacerbation, compared with 149/454 people (32.8%) in the placebo group (OR 0.75, p<0.05). The Committee noted the minimally clinically important difference was not highlighted for this outcome.

10.9. The Committee noted the secondary endpoints reported a significant improvement in FEV1 and FVC between the tiotropium and placebo groups, and in weekly morning and evening peak expiratory flow. Improvements in the ACQ-7 score and the Asthma Quality of Life Questionnaire (AQLQ) were reported in both study groups but the minimal clinically important differences were not reached in either trial. There were 16 patients hospitalised for asthma in the tiotropium group and 20 in the placebo group which the Committee noted was a non-significant difference, although members recognised the study was not powered to detect a significant difference.

10.10. The Committee reviewed Kew KM, Dahri K (Cochrane Database of Systematic Reviews, 2016 issue 1.Art.No:CD011721). Kew and Dahri reviewed three trials adding a long acting muscarinic acid (LAMA) to ICS/LABA versus ICS/LABA for adults with asthma – the two Kerstjens trials and a Japanese study by Ohta et al (Respirology 2014;19(supp3):65). The Committee noted that, in summary, the review considered that there are likely to be small added benefits of tiotropium 5 mcg daily on lung function and asthma control over ICS/LABA alone and fewer non-serious adverse events, but the effect was imprecise, and possible benefits on quality of life were negligible. The review considered the evidence of the effect on serious adverse events to be inconsistent.

10.11. The Committee noted a retrospective review of medical records by Price et al (Asthma Allergy 2015;8:1-13). The authors reviewed the medical records of patients aged 18 years and older with asthma who appear to have been prescribed tiotropium without a COPD diagnosis between the years 2001-2013 in the UK. The authors reviewed the medical records of 2,042 patients for the 12 months before and the 12 months after the date of the patient's first prescription of tiotropium. The Committee noted 93% of these patients were prescribed the dry powder formulation and 7% were prescribed the soft mist inhaler. The authors found that the proportion of patients having at least one exacerbation decreased by 10% (39.1% at baseline compared with 29.5%; p<001); and the proportion of patients having at least one acute respiratory event decreased from 58% to 47% (p<0.001) in the tiotropium prescribed group. The Committee considered the limitations of this study are its poorer internal validity, it being an observational design without a comparator group, no randomisation, absence of spirometry to confirm asthma or COPD, and the likely inclusion of patients with 'uncoded' COPD, while its strengths were in its external validity (generalisability and relevance), it being 'real world research' and patients with co-morbidities and smokers were included.

10.12. Other studies reviewed by the Committee included Ohta et al (Respirology 2014;19(supp3):65), NICE recommendation 2014, Kate McKeage (Adis Drug Review 2015) and those included in the suppliers application.

10.13. The Committee noted that the 2016 Global Initiative for Asthma (GINA) recommend the addition of tiotropium by soft mist inhaler at step 4 of the treatment guideline for patients aged ≥ 12 years with a history of exacerbations.

10.14. In terms of benefits, the Committee considered that the two Kerstjens studies provided

strong evidence that tiotropium improves FEV1 in patients with poorly controlled asthma on high dose ICS/LABA therapy, but also considered the clinical significance of this increase in FEV1 to be uncertain and below the minimally perceived patient improvement (FEV1 of 230ml corresponding to a reduction in SABA use of 0.81 puffs per day Santanello et al ERJ 1999;14:23-7 . The Committee noted that there were no head-to-head comparator trials with other add-on therapies (such as doubling the ICS dose in patients already taking a LABA, changing to an extrafine ICS or theophylline or oral corticosteroids). The Committee noted that the applicant had considered that some of these other therapy options for severe asthma were not evidence based or presented unacceptable clinical risk.

10.15. 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. **[withheld interim, pending review]** 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.

10.16. In summary, the Committee considered that there was high quality, moderate strength evidence from well conducted clinical trials for an improvement in FEV1 when tiotropium is added to an ICS/LABA in the treatment of patients with severe asthma. The Committee considered patient focused outcomes (frequency of exacerbations and the number of exacerbations) favour the addition of tiotropium over placebo, but the confidence intervals for both do not rule out no effect and the change in FEV_1 was substantially less that what has been shown to be the minimal patient perceived difference (Cochrane Review). In the 48 week trials, the time to first exacerbation was increased by 56 days with tiotropium compared with placebo (HR 0.79, 95%CI 0.62-1.00, p=0.03) and median time to first worsening of asthma was increased by 134 days (HR 0.69; 95%CI 0.58-0.82; p<0.001). Improvements in the CQ-7 and AQLQ scores were seen but the minimal clinically important difference was not achieved and there was no difference in hospitalisations.

10.17. The Committee noted that asthma is a major issue in New Zealand and that there is an unmet health need in treating asthma in general in adults due to factors such as poor health literacy, over prescribing of some agents and under prescribing of ICS, and low adherence. However the Committee was generally unsupportive of the application due to what it considered to be potential **[withheld interim, pending review]** safety risks with tiotropium Respimat being used in what is a diverse population of patients with many therapeutic options, balanced against the limited evidence of clinical benefits reported by the clinical trials.

10.18. The Committee recommended the application be declined.

11. Ruxolitinib for myelofibrosis

Application

11.1. The Committee considered a funding application from Novartis New Zealand Limited (Novartis) for a new listing of a Janus Associated Kinase (JAK) inhibitor, ruxolitinib, for the treatment of myelofibrosis in the Pharmaceutical Schedule.

Recommendation

11.2. The Committee **recommended** that ruxolitinib for the treatment of high risk and intermediate-2 risk myelofibrosis, be funded with a medium priority.

11.3. The Committee **recommended** that ruxolitinib for the treatment of intermediate-1 risk myelofibrosis, be funded with a low priority.

11.4. The Committee **recommended** that the funding application be referred to the

Haematology Subcommittee for further advice, particularly on the expected patient numbers, current treatments in New Zealand, ruxolitinib withdrawal syndrome incidence and management, and the development of Special Authority criteria.

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

Discussion

11.6. The Committee noted that the currently registered indication for ruxolitinib is for treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

11.7. The Committee noted ruxolitinib is an inhibitor of JAK1 and JAK2. The Committee noted that JAKs mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK signalling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK/STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells. The Committee considered the doses referenced by NICE (March 2016) would most likely reflect practice in New Zealand if funded.

11.8. The Committee considered that the health need of patients with high risk and intermediate-2 risk myelofibrosis was significant. The Committee noted that two-thirds of patients have constitutional symptoms. There are very limited alternative treatment options available, evidenced by their low use in the control group of the COMFORT-II randomized controlled trial (Harrison et al. N Engl J Med. 2012;366:787-98). The Committee noted that bone/muscle pain, fatigue/inactivity, pruritis, early satiety, night sweats and abdominal pain were common (Gimenez et al. J Med Econ. 2014;17:435-41; Mitra et al. Cancer Med. 2013;2:889-98).

11.9. The Committee noted the COMFORT-I randomised double-blind placebo-controlled trial (Verstovsek et al. N Engl J Med. 2012;366:799-802). This compared the efficacy of twice-daily oral ruxolitinib versus placebo in reducing spleen volume in patients with intermediate-2 (38.2%) or high-risk (61.2%) myelofibrosis (classified according to a 2008 International Prognostic Scoring System [IPSS]) at 89 sites in the United States, Australia, and Canada. The Committee noted 50% of the participants had primary myelofibrosis and 60% had used hydroxyurea previously. The Committee noted 155 patients with a median age of 68 were commenced on either 15 mg twice daily (platelet count of 100-200×109/L) or 20 mg twice daily (platelet count of >200×109/L). The median spleen volume was more than 2500 cm3 (>10 times the median normal spleen volume of 200 cm3).

11.10. The Committee noted the primary end point in COMFORT-I was the proportion of patients with a reduction in spleen volume of 35% or more at 24 weeks, assessed by means of magnetic resonance imaging (MRI). Secondary end points included the durability of response, changes in symptom burden (assessed by the total symptom score) and overall survival. Patients allocated to the placebo arm were eligible to crossover to ruxolitinib treatment if splenomegaly worsened. The primary end point was reached in 41.9% of patients in the ruxolitinib group as compared with 0.7% in the placebo group (P<0.001).

11.11. The Committee noted that among the patients for whom baseline and week 24 data were available, the 139 patients receiving ruxolitinib had a mean reduction in spleen volume of 31.6% (median, 33.0%) at week 24; the 106 patients receiving placebo had a mean increase of 8.1% (median, 8.5%). The reduction in spleen volume was durable in 67% (95% CI, 46.4 to 81.1) for 48 weeks or more of those who had an initial 35%

reduction in spleen volume. A survival analysis based on a planned data cut-off (with median follow-up, 51 weeks) revealed a significant survival advantage for patients who received ruxolitinib, with 13 deaths in the ruxolitinib group (8.4%) and 24 deaths in the placebo group (15.6%) (hazard ratio, 0.50; 95% CI, 0.25 to 0.98; P = 0.04). The rate of discontinuation of the study drug because of adverse events was 11.0% in the ruxolitinib group and 10.6% in the placebo group. Among patients who received ruxolitinib, anaemia, thrombocytopenia and diarrhoea were the most common adverse events.

11.12. The Committee noted a cohort study based on participants in COMFORT-I, after a median of three years, (Verstovsek et al. Haematologica. 2015;100:479-88). At data cut-off, approximately 50% of patients originally randomized to ruxolitinib remained on treatment, whereas all patients originally assigned to placebo had discontinued or crossed over to ruxolitinib. The mean percentage reduction in spleen volume from baseline was 31.6% at week 24 (median 33.0%) compared with 34.1% at week 144 (median 38.4%). Of the patients with a ≥35% spleen volume reduction by week 12, 53% still maintained this volume reduction after an additional 132 weeks. The median follow-up for the ruxolitinib arm was 149.1 weeks compared with 149.3 weeks for the placebo arm. The hazard ratio for overall survival when unadjusted for cross-over favoured patients originally randomized to ruxolitinib (hazard ratio 0.69 [95% CI 0.46-1.03; P=0.067) but did not reach statistical significance. The result was similar with adjustment for cross-over using a RPSFT method (hazard ratio 0.36 [95% CI 0.20-1.04]).

11.13. The Committee noted the open-label COMFORT-II trial which was a randomized controlled trial that compared the efficacy of twice-daily oral ruxolitinib versus best available therapy (BAT) (Harrison et al. N Engl J Med. 2012;366:787-98). Participants were stratified according to prognostic score at enrolment and were randomly assigned, in a 2:1 ratio to twice-daily oral ruxolitinib versus BAT. 50% of the participants had primary myelofibrosis and 70% had used hydroxyurea previously. The Committee noted that of the 146 patients who commenced on ruxolitinib, 40% had intermediate-2 and 60% had high-risk myelofibrosis by an updated IPSS scoring system. Patients commenced on ruxolitinib at either 15 mg twice daily (platelet count <200×109/L) or 20 mg twice daily (platelet count of >200×109/L).

11.14. The Committee noted the primary end point was the proportion of patients with a reduction in spleen volume of 35% or more at a 48 weeks (compared with 24 weeks in COMFORT-I), assessed by MRI (or CT if MRI unsuitable). Secondary end points included the length of time that a reduction in spleen volume of at least 35% was maintained, the time to a reduction in spleen volume of 35% or more from baseline, progression-free survival, leukaemia-free survival, overall survival, and change in marrow histomorphologic features.

11.15. The Committee noted the primary end point was reached in 28% of patients in the ruxolitinib group as compared with 0% in the placebo group (P<0.001). Among the patients for whom baseline and week 24 data were available, the patients receiving ruxolitinib had a mean reduction in spleen volume of 29.2% (median, 33.0%) at week 24; the patients receiving best available treatment had a mean increase of 2.7%. At week 48, patients treated with ruxolitinib had a mean decrease in spleen length from baseline of 56%, as compared with a mean increase of 4% in patients receiving the best available therapy.

11.16. The Committee noted that in the analyses of leukaemia-free survival and overall survival, there were 10 events in total (all of which were deaths): 6 events (4%) with ruxolitinib, as compared with 4 events (5%) with the best available therapy. The hazard ratio for leukaemia-free survival with ruxolitinib was 0.65 (95% CI: 0.18 to 2.31); while the hazard ratio for overall survival was 0.70 (95% CI: 0.20 to 2.49). In a time-to-event analysis, conducted at week 48, there were 44 (30%) patients in the ruxolitinib group

who had progression events, as compared with 19 (26%) in the group receiving the best available therapy, with an estimated hazard ratio for progression with ruxolitinib of 0.81 (95% CI: 0.47 to 1.39).

11.17. The proportion of patients who discontinued treatment owing to adverse events was small in both groups (8% in the ruxolitinib group and 5% in the best-available-therapy group), although adverse events of any grade requiring dose reductions or interruptions occurred more frequently with ruxolitinib than with the BAT (in 63% of patients vs. 15%). The most common haematologic abnormalities of grade 3 severity or higher (according to the National Cancer Institute's Common Toxicity Criteria, version 3) in either group were thrombocytopenia and anaemia, which were managed with a dose reduction, interruption of treatment, or transfusion. The Committee noted that during the treatment period, more patients in the ruxolitinib group than in the BAT group received at least one transfusion of packed red cells (51% vs. 38%).

11.18. In a follow-up of COMFORT-II after a median of three years (Cervantes et al. Blood. 2013;122:4047-53) a planned analysis assessed long-term efficacy and safety of ruxolitinib after a median follow-up of 151 weeks. Overall, 73% of patients (106 of 146) in the COMFORT-II ruxolitinib arm and 62% (45 of 73) in the BAT arm entered the extension phase to receive ruxolitinib. 45% (66 of 146) of those originally randomized to ruxolitinib remained on treatment, whereas all patients originally assigned to placebo had discontinued or crossed over to ruxolitinib. The Committee noted that initial spleen reductions of ≥35% obtained with ruxolitinib were sustained in many patients with continued therapy, however the median duration of response was not reached within the trial period. The Kaplan-Meier estimated probabilities of maintaining a spleen response at week 144 was calculated at 50% (95% CI, 36 to 63). Six patients achieved a spleen reduction of ≥35% after the primary analysis at week 48. The Committee noted adverse event rates in the group randomised to ruxolitinib including diarrhoea (15 per 100 patient years), fatigue (11 per 100 patient years) and pruritis (5 per 100 patient years).

11.19. The Committee noted that after five years of follow-up COMFORT-II (Harrison et al. Leukemia. 2016;30:1701-7) the median overall survival was not reached in the ruxolitinib arm and was 4.1 years in the BAT arm. The Committee noted there was a 33% reduction in risk of death with ruxolitinib reported when compared with BAT by intent-to-treat analysis (hazard ratio 0.67 [95% CI: 0.44 to 1.02; P=0.06]); while the crossover-corrected hazard ratio was 0.44 (95% CI: 0.18 to 1.04; P=0.06), although both of these were noted to be not statistically significant. The Committee noted there were no unexpected increases in the incidence of adverse events.

11.20. The Committee noted a pooled analysis of overall survival in COMFORT-I and COMFORT-II (Vannuchi et al. Haematologica 2015;100:1139). The Committee considered overall this was a poorly described analysis, although details of the model were unclear and in particular whether the trial source of the patients was treated as a fixed effect in the analysis. The Committee noted the hazard ratio of 0.65 (95% CI: 0.46 to 0.90; P=0.01) favoured ruxolitinib, with 144-week survival of 78% in the ruxolitinib group, 61% in the intention-to-treat control group and 36% in a crossover-adjusted control group.

11.21. The Committee noted a cohort study and related extension study (Verstovsek et al. NEJM 2010;363:1117, Verstovsek et al. Blood 2012;120:1202) of 153 and 158 patients respectively with myelofibrosis and past treatment or splenomegaly (92%). The mean age was 65, 63% were male and nearly all had intermediate-2 or high risk myelofibrosis. Participants were followed for a median of 15 months. The Committee noted 107 of the 158 enrolled in one of the two study centres. 54% of participants remained on ruxolitinib after three years. Overall survival favoured ruxolitinib compared to a historical control resulting in a hazard ratio of 0.58 (95% CI: 0.39 to 0.85; P=0.005).

11.22. The Committee noted a large cohort study (Al-Ali et al. Haematologica. 2016;101:1065-73) examining the safety and efficacy of ruxolitinib in 1,144 patients. The Committee noted this trial included a separate group with intermediate-1 risk disease and splenomegaly. A separate analysis of 163 patients with intermediate-1 risk myelofibrosis (a population of patients not included in COMFORT-I or COMFORT-II studies) found that after weeks 24 and 48, 56.9% and 62.3% of evaluable patients, respectively, achieved a ≥50% reduction from baseline in palpable spleen length. Most patients (69%) experienced a ≥50% reduction in spleen length at any time by week 48. Of the intermediate-1 risk patient group, 63.8% and 60.5% of patients achieved a ≥50% reduction from baseline in palpable spleen length at weeks 24 and 48 respectively. The Committee considered that this study provided some evidence that those with intermediate-1 disease would also gain benefit in terms of a reduced spleen size, although the degree of that benefit will likely be smaller than those with more severe disease.

11.23. The Committee noted a small cohort study by Mead et al. (Br J Haematol. 2015;170:29-39) in 48 patients with myelofibrosis, including 14 intermediate-1 risk patients if they had a palpable spleen measuring ≥5 cm from the costal margin. The Committte noted this study identified a health utility index score of 0.72 measured by EQ-5D which improved by 0.06 on ruxolitinib treatment.

11.24. The Committee considered that the potential for ruxolitinib withdrawal syndrome was not well addressed in the application but it could be significant. The Committee noted the Data Sheet recommends gradual tapering of the dose on withdrawal and the British Committee for Standards in Haematology Guidelines (Reilly et al. Br J Haematol. 2014;167:418-20) suggests both gradual tapering and to also treat patients undergoing ruxolitinib withdrawal with systemic glucocorticoids.

11.25. The Committee considered that two large randomized-controlled trials, one against BAT, provide high quality evidence of strong effect for a health benefit associated with reduced spleen size for those with intermediate-2 or high-risk disease and marked splenomegaly. The Committee further considered there was moderate to high quality evidence for a moderate effect on some disease-related quality of life measurements including global health status, fatigue, role functioning, and physical functioning, and weak evidence of a survival benefit. The Committee further noted that the estimates of effect were confounded by cross-over to active therapy.

11.26. The Committee considered that the evidence provided for an association between a reduction in splenomegaly and improved overall survival was weak. The Committee considered that supportive care for severe myelofibrosis such as transfusions and frequent monitoring would still be required in patients taking ruxolitinib.

11.27. The Committee considered it plausible that those with intermediate-1 disease would gain a health benefit from ruxolitinib. However, the Committee considered that given the generally lower health need of this group, the lack of high-quality evidence, such as randomized controlled trials specifically in this population, and the comparatively smaller benefits expected, it was appropriate to recommend funding ruxolitinib for this group with a lower priority.

12. Sodium hyaluronate and sodium chondroitin sulphate prefilled syringe for painful bladder syndrome and interstitial cystitis

Application

12.1. The Committee considered a funding application from Juno Pharmaceuticals NZ Limited for the new listing of the iAluRil device, sodium hyaluronate (1.6%-800 mg/50 mL) and sodium chondroitin sulphate (2%-1 gm/50 mL) 50 mL prefilled syringe for the following indications:

- patients with Painful Bladder Syndrome and Interstitial Cystitis (PBS/IC) who have failed other hospital based conventional and invasive treatments;
- patients with recurrent urinary tract infections (rUTIs); more than 3 urinary tract infections within 9 months with symptoms of urgency, frequency and bladder pain;
- radiation or chemically induced cystitis following chemotherapy, radiation therapy or Bacillus Calmette-Guerin (BCG) treatment.

Recommendation

12.2. The Committee **recommended** that the application for the iAluRil device for patients who failed conventional treatment for painful bladder syndrome be declined.

12.3. The Committee **recommended** that the application for the iAluRil device for patients with recurrent urinary tract infections (rUTIs), who had more than 3 urinary tract infections within 9 months with symptoms of urgency, frequency and bladder pain be declined.

12.4. The Committee **recommended** that the application for the iAluRil device for patients with radiation or chemically induced cystitis following chemotherapy, radiation therapy or Bacillus Calmette-Guerin (BCG) treatment be declined.

12.5. The Committee noted that they would consider reviewing its recommendations if new evidence was submitted.

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

Discussion

12.7. The Committee noted that the iAluRil device, sodium hyaluronate (1.6%-800 mg/50 mL) and sodium chondroitin sulphate (2%-1 gm/50 mL) 50 mL prefilled syringe, was designed to restore the glycosaminoglycans (GAGs) of the bladder mucosa surface layer. Members noted that GAGs are a class of mucopolysaccharides with hydrorepellent properties which assist in preventing urinary toxic agents from penetrating the bladder wall which, when allowed to penetrate, could be one cause of interstitial cystitis/painful bladder syndrome (IC/PBS). Members considered that the pathology of IC/PBS was poorly understood and damage to the GAG layer of the bladder was only one of many possible causes of bladder inflammation.

12.8. The Committee noted that there was no New Zealand data on the number of patients with IC/PBS provided, although it considered that the number of patients was likely to be significant. Members considered that the patient numbers for the rUTIs group was likely underestimated, as according to BPAC NZ the prevalence could be as high as 17,000 patients, based on approximately 50% of women experienced at least one UTI in their lifetime, and one in four UTIs experiencing recurrent infections.

12.9. The Committee reviewed the following studies regarding quality of life data for patients with IC/PBS:

- Michael et al. QOL among women with IC. J Urol 2000; 2:423-427;
- Meijlink. Interstitial Cystitis – Bladder Pain Syndrome. IPBF. ISBN: 90-810327-1-2. 2016;
- Clemens et al. *Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women.* J Urol. 2007; 4:1390-4.

12.10. Members considered that patients with PBS had a high health need, as with other chronic pain syndromes, as the condition could affect their ability to undertake usual daily activities and sleep through the night due to the frequency and urgency of the need to urinate. Members noted that there is a high prevalence of anxiety and depression in

this population. Members noted that currently available treatments, such as *dimethyl sulfoxide (*DMSO), for PBS were for symptom management.

12.11. The Committee considered that there was significant overlap between the IC patient group and those with recurrent urinary tract infections (rUTIs), though it was difficult to define the two groups as patients with rUTIs could sometimes present with symptoms of a UTI but sterile urine on microscopy. A Member noted that people with recurrent UTIs may be initiated on prophylactic antibiotic treatment, and this could be initiated early in primary care settings. Members noted that rUTIs may lead to the development of chronic pain in some patients which, once developed, can lead to significant deterioration in quality of life.

12.12. The Committee reviewed prevalence data on chemical and radiation induced cystitis from Payne et al. (BJU. 2013;112:885-97), and noted that the most frequently reported causal factors were radiotherapy to the pelvic area, where haemorrhagic cystitis had been reported in up to 20% of patients while treatment with cyclophosphamide and BCG had a reported incidence of up to 30% of patients. Members noted that in New Zealand these figures would equal approximately 10 patients per year.

12.13. The Committee considered the evidence for the use of iAluRil and noted that most of the studies involved small patient numbers. All of the studies were conducted in Europe and used variable dosing regimens. The Committee considered that the quality of the evidence for the use of iAluRil was of poor to moderate quality, with the majority of studies being open-label, retrospective cohort or small placebo-controlled trials.

12.14. Members reviewed the following studies in patients with IC/PBS:

- Cervigni et al. A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis. Neurology Urodynamics. 2016. Sep 21. doi: 10.1002/nau.23091
- Porru et al. Impact of intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2012; 9:1193-99.
- Gilberti et al. Combined intravesical sodium hyaluronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndrome: a prospective study. Ther Adv Urol. 2013;4:175-9.
- Morelli et al. Hyaluronic acid chondroitin sulphate: a potential factor to select pure stress urinary incontinence in patients with interstitial cystitis/painful bladder syndrome and mixed incontinence symptoms. Mirerva Gineol. 2015; 67:121-5.
- Torella et al. Intravesical therapy in recurrent cystitis: a multi-centre experience. J Infect. Chemother. 2013;5:920-5.
- De Vita et al. Effectiveness of intravesical hyaluronic acid and chondroitin sulfate in recurrent bacterial cystitis: a randomized study. Int Urogynecol J 2012;12: 1707-13.

12.15. Members reviewed the following studies in patients with chemical or radiation induced cystitis:

- Creta et al. Intravesical instillation of hyaluronic acid and chondroitin sulphate for Bacillus Calmette-Guerin induced chemical cystitis. 85th Italian Society of Urology (SIU) Congress, Venice, Italy 21-24 Oct 2012.
- Gacci et al. Bladder instillation therapy with hyaluronic acid and chondroitin sulphate improves symptoms of post radiation cystitis: prospective pilot study. Clin Genitourin Cancer. 2016 Oct;5:444-9.

12.16. Members reviewed the following studies in patients with rUTIs:

- Damiano et al. Prevention of recurrent urinary tract infections by intravesical

administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomized trial. Eur Urol. 2011;4:645-1.

- Cicione et al. Intravesical treatment with highly concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multi-center study. Canadian Urol. Assoc. J. 2014;9-10:E721-7.

12.17. The Committee noted that Cervigni et al was an open-label randomised controlled trial with 110 participants with a primary end point in the difference in pain level on the Visual Analogue Scale (VAS) from baseline to 6 months (end of follow-up). Patients (110 women) were randomised using a 2:1 allocation ratio to receive 13 weekly instillations of iAluRil (n = 74) or DMSO 50% (n = 36). Members noted that the study reported a statistically significant pain decrease in both groups at the 3-month end-of-treatment visit with a VAS score reduction of -39.27 (SD 24.52) for iAluRil and of -31.00 (SD 26.38) for DMSO 50%. At the 6-month follow up 73% of iAluRil and 58% of RIMSO-50 groups had a 30% VAS reduction from baseline. Approximately twice as many of the RIMSO-50 group reported adverse events compared to the iAluRil group (30.56% and 14.86% respectively); however, one patient in each group withdrew, both due to treatment-related effects. The Committee noted that there was no difference between the two groups on secondary end points and that the regimen used was for a shorter duration than specified in the supplier's application.

12.18. The Committee noted that Cicione et al was a retrospective cohort study involving seven European institutions assessing the effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulphate as a non-antibiotic treatment option for prophylaxis of recurrent urinary tract infections (rUTIs) in female patients. Members noted that the study included 157 patients who had received nine instillations of iAluRil (weekly for four weeks and then monthly for five months) between January 2010 and March 2012 which was a different treatment regimen from the one recommended by the supplier. Members further noted that there were a large number of patients who dropped out before reaching the final follow-up at 24 months (81 patients were recorded at 18 months and 41 patients were recorded at 24 months out of an original 157 patients) and no explanation was given for the dropouts. Members noted that the percentage of patients with UTIs at baseline was not specified.

12.19. The Committee noted that given the variable regimens used in the clinical studies of iAluRil, it is difficult to determine how many instillations patients would require and noted it was possible that some patients could potentially use the treatment indefinitely. Members considered that placebo/blinding was likely to be an issue in the clinical trials based on anecdotal evidence from local experts in Christchurch.

12.20. The Committee considered that, if listed on the Pharmaceutical Schedule, iAluRil is most likely to be prescribed by urologists due to the difficulties associated with diagnosis of non-infective PBS, that may involve an inflammatory process, following presentation with pelvic pain. The Committee considered that most patients currently receive d*imethyl sulfoxide (*DMSO) instillations 6-10 times per year. Members considered that iAluRil's use in the community would be constrained by patients' willingness to self-catheterise and/or the capacity of community clinics to catheterise patients. Members noted that catheterisation in a clinic would be an additional cost to the health system. Members noted that, if listed on the Pharmaceutical Schedule, the cost of funding iAluRil is likely to be significant.

12.21. The Committee considered the evidence to support use of iAluRil in PBS was of low strength and quality. The Committee noted that the studies were open-label, involved small participant numbers, had differing treatment regimens and the results reported wide confidence intervals. The Committee considered that the evidence for use of iAluRil in rUTIs and IC was of poor quality, and mainly limited to retrospective cohort studies and a small placebo-controlled trial. The Committee considered that although there is some evidence of a trend towards a beneficial effect of iAluRil for PBS, the

Committee considered this evidence was currently insufficient to recommend the treatment for Schedule listing. The Committee noted that more evidence would likely emerge and it would review its recommendations if new, supportive clinical trial evidence became available.