Transplant Immunosuppressant Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 3 October 2017

(minutes for web publishing)

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

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

The Transplant Immunosuppressant Subcommittee 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.

These Subcommittee minutes was reviewed by PTAC at its meeting on 9 & 10 August 2018, the record of which will be available in due course.

Record of the Transplant Immunosuppressant Subcommittee meeting held at PHARMAC on 3 October 2017

1 Record of previous minutes

1.1 The Subcommittee noted the record of the previous meeting that took place on 11 May 2015 and accepted that they were an accurate record of the meeting.

2 Updated NPPA policy

2.1 The Subcommittee noted a presentation by PHARMAC staff on the updated Exceptional Circumstances framework and the updated Named Patient Pharmaceutical Assessment (NPPA) application process online.

2.2 The Subcommittee noted that the NPPA policy does not include a clear definition for how unique a patient needed to be to be considered for funded treatments via the NPPA process.

2.3 The Subcommittee noted that evidence of efficacy for a non-funded treatment through a patient self-funded trial or a compassionate supply by a supplier would not be considered by PHARMAC during the NPPA assessment. The Subcommittee also noted information from PHARMAC staff that doing so may create an inequity of access due to some patients not being in a position to trial a treatment first. Members considered that while this rationale was understandable, it was also important to consider evidence from a real-world-setting as part of the NPPA assessment process.

3 Factors for Consideration

3.1 The Subcommittee noted a presentation by PHARMAC staff outlining PHARMAC's new decision-making criteria, the Factors for Consideration (FFC), which replaced the previous nine Decision Criteria on 1 July 2016. Members noted that all recommendations made by the Subcommittee should be now provided in the context of the FFC.

3.2 The Subcommittee considered that the wheel presentation of the FFC was an improvement over the previous nine Decision Criteria list.

4 Therapeutic Group Review

Previous recommendations and action points

Alemtuzumab

4.1 The Subcommittee noted that alemtuzumab was not currently used in the New Zealand transplant immunosuppressant setting.

4.2 The Subcommittee noted that following the withdrawal of the 30mg/ml infusion presentation worldwide, alemtuzumab was available for compassionate use only with restricted distribution for some indications. Members noted that a low strength 10mg/ml alemtuzumab product was now marketed for multiple sclerosis. Members considered that PHARMAC staff could report back if a supply was identified, however it did not need to remain an active action point.

Tacrolimus

4.3 The Subcommittee noted that tacrolimus for non-transplant indications had been ranked by PHARMAC and remained an option for investment pending available funding. Members noted that this was for oral use only and that the Dermatology Subcommittee was reviewing an application for tacrolimus for topical use.

Transplant Immunosuppressant pharmaceuticals

Community Expenditure and Usage

4.4 The Subcommittee noted that gross expenditure in the community for the main transplant immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin, sirolimus and tacrolimus) was approximately $10.75 million for the financial year ending (FYE) June 2017, an 8% increase on the previous year but down 30% over the last 5 years. The Subcommittee also noted that the expenditure change is mainly due to volume increase in tacrolimus, mycophenolate and ciclosporin, with price decreases for azathioprine and sirolimus.

Ciclosporin

4.5 The Subcommittee noted that there is potential for competition in the ciclosporin market, however due to differences in bioavailability, each product would need to be considered by the Subcommittee to determine if it was appropriate. Members noted PHARMAC could use a Request for Information to seek product details and availability prior to determining the next commercial steps.

4.6 The Subcommittee considered that if there were to be a change in brand of ciclosporin in the future then it would be appropriate to use the same approach used for the tacrolimus brand change. Members noted a ciclosporin brand change could be more challenging than tacrolimus because with no current restrictions (no Special Authority) required it would be more difficult to track patients requiring additional monitoring, such as transplant patients.

Sirolimus

4.7 The Subcommittee noted a trend towards using sirolimus in children and young adults receiving ciclosporin or tacrolimus due to the adverse effects such as eosinophilic oesophagitis and eczema.

4.8 The Subcommittee considered that though sirolimus is a small market with only 71 current transplant patients, it is essential to maintain access to sirolimus as an alternative immunosuppressants for transplant patients. Members noted there is recent growth in using sirolimus for other indications.

4.9 The Subcommittee noted everolimus is currently funded for patients with tuberous sclerosis and sub-ependymal giant cell astrocytomas (SEGAs). Members noted PHARMAC receive a number of NPPA applications for sirolimus or everolimus for other tuberous sclerosis indications and these may be considered for schedule listing in the future.

Tacrolimus

4.10 The Subcommittee noted the sole supply for Tacrolimus Sandoz is due to end 31 October 2018 and PHARMAC are exploring commercial options for further price reductions in this market.

4.11 The Subcommittee noted that Sandoz has two new strengths of tacrolimus capsules that could be made available in New Zealand, a 0.75mg capsule and a 2mg capsule. The Committee considered the 0.75mg capsule could be helpful for dose adjustments for patients requiring low doses and were supportive of this strength being made available on the Schedule. The Subcommittee did not consider there was any clinical need for a 2mg capsule and having multiple strengths could add more risk and make it more confusing for patients.

Basiliximab

4.12 The Subcommittee noted there had been a black box warning regarding the off-label use of basiliximab in heart transplantation (http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con465930.pdf). The Subcommittee noted this information is now included in international product datasheets, noting increased cardiac related mortality with use of basiliximab compared to other induction agents. Members noted this raises medical-legal issues to consider. However, members also noted that basiliximab was widely used internationally for transplantation of different organs. Members considered that clinical evidence was required to demonstrate it was less safe to use in order to drive a change in current practice. Members noted New Zealand transplant services continue to use basiliximab induction therapy in selected patients, including in cardiac transplant. Basiliximab is used to delay initiation of tacrolimus in cardiac patients.

4.13 Members noted that the benefits of using basiliximab for induction in some patient groups are unclear, particular in low risk patients and kidney transplantation. Auckland DHB plan to review it's use of basiliximab in renal transplantation. Members noted that if basiliximab is not used, then there may be an increase in usage of anti-thymocyte globulin for induction.

Other pharmaceuticals related to transplant

Antivirals

Valganciclovir

4.14 The Subcommittee noted valganciclovir is included in the upcoming 2017/18 Invitation to Tender (ITT) with further price reductions expected.

Antifungals

Voriconazole

4.15 The Subcommittee noted that it had previously discussed a pending clinician funding application for voriconazole for use in lung transplant patients. Members noted this was no longer required as use in this group is covered by the current Special Authority criteria.

Liposomal amphotericin and caspofungin

4.16 The Subcommittee noted the liposomal amphotericin is used as prophylaxis post liver transplant in patients that have further abdominal surgery.

Vaccines

4.17 The Subcommittee noted the Immunisation Subcommittee recently reviewed all the current criteria for special groups.

Zoster vaccine

4.18 The Subcommittee noted that PHARMAC has released a consultation regarding the possible funding of the zoster vaccine (Shingles) from 1 April 2018. Members noted that the proposed criteria did not include any high risk groups such as transplant patients. Members considered the use of zoster vaccine in the transplant population should be considered for patients under 65 years of age. The Subcommittee noted that the American Society of Transplantation guidelines (Am J Transplant 2013;13:311-7) support use of zoster vaccine pre-transplantation, even though there is no evidence to suggest that vaccination will reduce the risk of varicella zoster virus reactivation post-transplant or whether it will be effective in those under 50 years of age. Members noted that they recommended their patients have zoster vaccination if they are varicella antibody negative pre transplant. Members noted varicella vaccine (chickenpox vaccine) is funded for transplant patients (prior to transplant and if immunosuppressed and considered appropriate).

4.19 The Subcommittee noted evidence is very limited in transplant patients, but they were supportive of using zoster vaccine in this group where appropriate. The Subcommittee **recommended** PHARMAC staff seek a clinician funding application to consider widening access to zoster vaccine for immunocompromised patients (including transplant patients) who are varicella antibody negative. Members noted this would be considered by the Immunisation Subcommittee of PTAC.

NPPA review

4.20 The Subcommittee noted a report of NPPA applications received for transplant immunosuppressants and other related treatments between June 2015 and August 2017.

Looking forward

4.21 The Subcommittee noted that belatacept is now widely available internationally, however no application has been submitted in New Zealand to Medsafe or PHARMAC. The Subcommittee considered that PHARMAC staff should follow-up with the suppler, BMS, regarding submitting to New Zealand.

4.22 Members noted the biosimilar rituximab is likely to be available soon and noted that PHARMAC were looking at opportunities in this market.

4.23 The Subcommittee noted that at its last meeting, members noted bortezomib was being investigated for use in renal transplant rejection. Members noted the evidence for this

agent for acute humoral rejection was very limited and the Subcommittee were no longer interested in reviewing this product for use in the transplant setting.

5 Matters Arising and Correspondence

HPV vaccine

5.1 The Subcommittee noted the recent listing of the 9-valent human papillomavirus vaccine (HPV9, Gardasil 9).

5.2 The Subcommittee noted that the vaccine was primarily used for the prevention of human papillomavirus (HPV) infection and subsequent related cancers. Members noted that the vaccine may also have a therapeutic effect in the treatment of widespread HPV infection.

5.3 The Subcommittee noted the current funding criteria for the HPV9 means that any transplant recipients (pre or post transplant) between 9 and 26 years of age inclusive are eligible for three funded HPV9 vaccinations. Patients over 26 years of age are not currently funded, and this aligns with the approved Medsafe indication and study data of the vaccine for use in males up to 26 years of age. Members noted HPV9 vaccine is Medsafe approved in females aged 9 through 45 years, noting evidence of vaccine efficacy is based on core efficacy population of females aged 16 to 26 years and currently there is no data from studies of HPV9 related to females over 26 years of age.

5.4 Members noted the previous criteria for the 4-valent HPV (HPV4) vaccine included use in any transplant patients with no gender or age indications. This funding criteria was amended with the introduction of the new HPV9 vaccine and widening of access to include boys in January 2017.

5.5 The Subcommittee noted the Nephrology Subcommittee, at its December 2016 meeting, recommended the Transplant Immunosuppressant Subcommittee and the Immunisation Subcommittee consider the use of the HPV vaccine in patients pre/post transplantation who are over 26 years of age and are not currently funded.

5.6 The Subcommittee noted there is very limited data on HPV vaccination in solid organ transplant recipients, especially for individuals over the age indication. Primary prevention data was limited to animal models and anecdotal reports. Members noted the safety and efficacy of HPV vaccination (HPV4) in transplant patients up to the age of 35 was reported in a Phase III study of 50 patients who received 3 doses post-transplant (Kumar et al. Am J Transplant 2013;13:2411-7). The vaccine was considered to be safe and well tolerated, with suboptimal immunogenicity; reported to be 53% to 68% for the 4 viral types in HPV4.

5.7 Members considered that people over 26 years of age were very likely to be already infected with HPV.

5.8 The Subcommittee discussed the advantages of vaccination prior to transplant to prevent HPV infection and improved immunogenicity prior to immunosuppression (pre-transplant). Members noted the transplant patients have a higher risk of skin cancers and therefore have a high need for HPV vaccination. Increase in skin cancer rates are reported 3 to 5 years post-transplant, with differences in the ratio of squamous cell carcinoma (SCC) to basal cell carcinoma compared to the general population.

5.9 The Subcommittee noted several international clinical groups, SCOPE network (Skin Care in Organ Transplant Patients) and ITSCC (International Transplant Skin Cancer Collaborative) both recommend use of HPV vaccination in solid organ transplant for prevention and treatment of HPV and chemoprophylaxis of skin cancer.

5.10 The Subcommittee noted that current HPV vaccines do not protect against cutaneous HPV types causing benign skin warts, or against beta-papillomavirus types implicated in the development of non-melanoma skin cancer (NMSC) in immunosuppressed patients. Members noted that HPV vaccines based on L2 antigens (using an L2 minor capsid protein) are in development that may be effective across all HPV subtypes and could be a promising option in this patient group.

5.11 The Subcommittee considered that expert opinion supported the use of HPV vaccination, including HPV9, in transplant patients, including in patients over 26 years of age, based on unmet high health need and anecdotal evidence. Members noted that use of HPV9 vaccine in males over 26 years and females over 45 years would be unapproved indications.

5.12 The Subcommittee considered that any new published data or evidence should be considered at its next meeting and the Immunisation Subcommittee should also be asked for consider widening access for transplant recipients over the age of 26.

Tacrolimus

5.13 The Subcommittee noted the Paediatric Nephrology Service at Starship recently published their experience with the tacrolimus brand change for 37 paediatric kidney transplant recipients (Naicker et al. Pediatr Nephrol. 2017;32:2125-31).

6 Valganciclovir

Background

6.1 The Subcommittee reviewed correspondence from a member requesting consideration of widening access of valganciclovir to lung transplant recipients who require valganciclovir prophylaxis to prevent cytomegalovirus (CMV) reactivation when receiving steroid pulse therapy for late acute rejection.

Recommendation

7.3 The Subcommittee **recommended** that funding of oral valganciclovir be widened to include CMV prophylaxis for all transplant patients receiving pulse methylprednisolone for acute rejection after the initial course of CMV prophylaxis (variable depending on the organ) that requires a further 90 days of valganciclovir for CMV prophylaxis with a high priority.

7.4 The Subcommittee **recommended** that funding of oral valganciclovir be widened to include an additional 6 months of initial CMV prophylaxis for lung transplant patients (12 months total from time of transplant) if the quantiferon CMV-approach is used to determine prophylaxis requirement with high priority.

Discussion

7.5 The Subcommittee noted that valganciclovir is currently funded for a range of situations requiring CMV prophylaxis, including 3 months prophylaxis post-transplant for any solid organ transplant, 6 months prophylaxis for lung transplant recipients, and an additional 3 months prophylaxis for patients receiving anti-thymocyte globulin. Valganciclovir is also funded for the treatment of CMV disease in immunocompromised patients.

7.6 The Subcommittee noted that it had discussed this issue in May 2015 and recommended that the Special Authority be amended to include renewal criteria for patients who had undergone a lung transplant and received pulse methylprednisolone for acute rejection after the initial 6 months of CMV prophylaxis and requires a further 90 days of valganciclovir for CMV prophylaxis. Members noted that in 2015there was an unmet clinical need in this group and some clinicians were working around the Special Authority criteria in order to access treatment.

7.7 The Subcommittee noted that the Anti-infective Subcommittee considered a request to widen access to lung transplant patients receiving pulse methylprednisolone therapy in November 2015 and recommended that the application be declined based on the lack of data to support prophylaxis in this setting. Members noted that PTAC reviewed these minutes in February 2016 and deferred making a recommendation and requested that the Transplant Immunosuppressant Subcommittee reviewed the evidence in relation to the use of valganciclovir to prevent CMV reactions during steroid pulse therapy and also for the treatment or prophylaxis of Epstein-Barr virus prior to PTAC making a recommendation.

7.8 The Subcommittee noted that the lung is a major site of CMV latency and recurrence (Balthesen et al. J Virol 1993;67:5360-6) with likelihood of lung transplant recipients developing CMV infection being very high (54-92% in patients without prophylaxis). Lung transplantation is therefore associated with the transfer of a larger CMV viral load than other solid organs and, as a result, the risk of CMV infection and disease is greater than in other solid organ transplant recipients. This is the rational for the longer initial CMV prophylaxis in lung transplant compared to other organs. Members noted that CMV infection is associated with the development of bronchiolitis obliterans (BOS), one form of chronic lung allograft dysfunction. BOS is associated with decreased lung allograft and patient survival rates.

7.9 Members noted a multicentre randomised controlled trial in 136 patients (Palmer et al. Ann Intern Med. 2010;152;761-9) that reported extending prophylaxis with oral valganciclovir from 3 months to 12 months after lung transplantation to be efficacious. CMV disease occurred in 32% of the short-course group versus 4% of the extended-course group ($P < 0.001$). Significant reductions were observed with CMV infection (64% vs. 10%; $P < 0.001$) and disease severity (viral load 110 000 vs. 3200 copies/mL, $P = 0.009$) with extended treatment. Rates of acute rejection, opportunistic infections, adverse events, CMV UL97 ganciclovir-resistance mutations, and laboratory abnormalities were similar between groups. During the 6 months after study completion, a low incidence of CMV disease was observed in both groups.

7.10 A further sub-analysis of 38 randomised patients from one centre reported extending valganciclovir prophylaxis to 12 months provides a durable long-term CMV protective benefit compared with short-course therapy, without increasing adverse hematologic effects. During a mean follow-up of 3.9 years in each group, a sustained protective benefit was seen with a lifetime CMV incidence of 12% vs 55%, respectively (hazard ratio, 0.13;

95% confidence interval, 0.03-0.61; p = 0.009), an effect that persisted after adjustment for clinical risk factors (Finlen Copeland etal J Heart Lung Transplant 2011 (30:990-6).

7.11 Members noted the optimal length of CMV prophylaxis in lung transplant recipients according to CMV status has been the focus of a recent study (Monforte et al. Transplant Infectious Disease. 2017;19:e12694) that reported that prophylaxis length was an independent risk factor for CMV disease in this patient group. The study also noted that despite CMV prophylaxis, the incidence of CMV infection is still considerable in CMV-seropositive lung transplant recipients. A multicentre study of valganciclovir prophylaxis in CMV-seropositive lung transplant recipients (Monforte et al. Am J Transplant. 2009;9:1134-41) reported that treatment with glucocorticosteroid pulses was also an independent risk factor for the development of CMV infection or disease.

7.12 The Subcommittee noted that valganciclovir is also associated with adverse effects, the predominant one being neutropenia. Dose reductions to manage toxicity may be associated with the emergence of resistant strains of virus that are more difficult to treat.

7.13 The Subcommittee noted further diagnostic testing may help to assess the risk of CMV infection in lung transplant patients and could be used to direct prophylaxis for individual patients. In particular, assays that assess CMV-specific T cell immunity may help predict which patients are at increased risk of CMV disease following transplantation. These include QuantiFERON (QFN) CMV assays, ELISpot, MHC multimer staining and others. One study has demonstrated that solid organ transplant patients that demonstrated CMV-T cell immunity by QFN had a lower risk of CMV disease at 12 months post-transplant (Manuel, et al. Clin Infect Dis. 2013; 56:817-24). Kumar D et al (Am J Transplantation 2017;17:2468) recently reported an interventional study using cell-mediated immunity to personalise therapy for CMV infection post-transplant with the aim of reducing antiviral treatment and prophylaxis. An Australian study of QFN CMV-directed CMV prophylaxis versus standard of care to reduce late CMV reactivation in patients undergoing lung transplantation reported a QFN-CMV directed approach to antiviral prophylaxis significantly reduced the incidence of CMV reactivation within the lung allograft (37% vs. 58%; OR 0.41, 95% CI 0.19-0.92; p = 0.03) (Westall G et al. J Heart Lung Transplant 2017;36:S200-1 (Abstract)).

7.14 Members noted the significant cost impacts of treating a CMV infection, with patients requiring at least 3 months treatment at full dose (double the prophylaxis dose) and these patients may also then experience repeat episodes and require ongoing prophylaxis. Applied to the NZ setting, Members considered the QFN-CMV directed approach to prophylaxis could reduce valganciclovir usage by approximately 20% as well as reduce monitoring of CMV viral loads (costs approximately $350 per test), Members noted that QFN-CMV assays are approximately $100 per test.

7.15 The Subcommittee noted that quantiferon CMV testing will soon be used at Auckland District Health Board for lung transplant recipients, however would not be available in all DHBs. Members noted that this area is developing quickly and considered changes to the Special Authority criteria may need to be considered to incorporate this optional approach into treatment duration. Members noted this approach may apply to other solid organ transplant recipients in the future, particularly following treatment for CMV viraemia.

7.16 The Subcommittee considered that evidence supports the extension of CMV prophylaxis in lung transplant patients for a further 6 months in patients identified at risk with QFN-

CMV monitoring. The Subcommittee noted there were about 20 lung transplants per year and 17 of those received 6 months prophylaxis with approximately 2/3 requiring a further 6 months.

7.17 The Subcommittee noted the very limited evidence available to support the reintroduction of valganciclovir prophylaxis following augmented immunosuppression to treat acute rejection (either pulse steroid therapy or other increased immunosuppression), however it is standard practice internationally based on expert opinion and multivariant analysis that increased immunosuppression is an independent risk factor for CMV infection, particularly in lung transplant. Members noted that due to international practice using prophylaxis during steroid pulse therapy, there is not a group of patients in which to study and therefore further evidence is unlikely. Members considered that there is a high unmet health need in this population and estimated there would be approximately 5 lung transplant patients per year that may require this. Members noted that if access was widened to allow for up to 12 months initial prophylaxis in lung transplant then this would cover some of these patients, however rejection does also occur post 12 months following transplant. The Subcommittee considered that transplant patients receiving other biologic agents, such as rituximab, for rejection or post-transplant lymphoproliferative disease (PTLD), should also have access to valganciclovir for CMV prophylaxis, as they do following a course of anti-thymocyte globulin.

7.18 Members noted that the price of valganciclovir may reduce in the near future as a result of the tender process and considered that is would be clinically desirable to retain the Special Authority restrictions to guide appropriate practice, however acknowledged that restrictions were in place for fiscal management and targeting treatment to those that benefit most, not to provide clinical guidance.

7.19 The Subcommittee noted the treatment and prophylaxis of Epstein-Barr virus (EBV) with valganciclovir has been previously discussed by Nephrology Subcommittee. Members noted the EBV is associated with PTLD and this occurs in approximately 1% of transplants and ranges in severity from benign polyclonal lymphocytosis to highly malignant lymphomas. EBV is a common pathogen in most parts of the world as approximately 90 to 95% of adults show serologic evidence of infection. Members noted that the American Society of Transplantation Infectious Diseases Guidelines (Am J Transplant 2013;13:107-20) states that although some centres employ chemoprophylaxis and/or pre-emptive strategies using EBV viral load, published data in the form of prospective controlled trials in support of these protocols are currently limited and the role of antiviral agents is controversial. The Subcommittee considered evidence to support use of valganciclovir in this setting should be considered by this Subcommittee at a future meeting.