Transplant and Immunosuppressant Subcommittee of PTAC meeting

held 7 September 2012

(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 2008*.

Note:

- that this document is not necessarily a complete record of the Transplant Immunosuppressant Subcommittee meeting; only the relevant portions of the minutes relating to Transplant Immunosuppressant Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are published; and
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

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 were reviewed by PTAC at its meeting on 14 & 15 February 2013, the record of which will be available on the PHARMAC website in April 2013.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) to:

(i) enable PHARMAC to carry on, without prejudice or disadvantage, commercial activities (section 9(2)(i); and
(ii) enable PHARMAC to carry on, without predjudice or disadvantage, negotiations (including commercial and industrial negotiations)(section 9(2)(j).

1 Therapeutic Group Review

1.1 The Subcommittee considered a therapeutic group review paper from PHARMAC staff. Members noted that the paper covered several topics as follows:

- Transplant Immunosuppressant Therapeutic Group Review;
- Funding applications and pharmaceuticals of interest
- Exceptional Circumstances / NPPA review

Transplant Therapeutic Group Review

1.2 The Subcommittee noted that PHARMAC was considering a proposal to fund voriconazole and reviewed the proposed Special Authority as recommended by the Anti-infective Subcommittee of PTAC. Members considered that all applications should be from a multi-disciplinary team including an Infectious Disease Specialist. Members considered that a 3 month approval period, rather than the proposed 1 month would be more appropriate and recommended that the criteria be merged into one Special Authority.

1.3 The Subcommittee noted that PHARMAC was considering a proposal to fund posaconazole and reviewed the proposed Special Authority as recommended by the Anti-infective Subcommittee of PTAC. Members considered that the proposed criteria were appropriate.

1.4 The Subcommittee noted that recently, Sanofi had notified PHARMAC, and the haematology community, that from 3 September 2012 alemtuzumab (MabCampath) would no longer be available for commercial sale. Members noted that patients with CLL would be able to continue to access alemtuzumab through an "Access Program". Members noted that alemtuzumab was used overseas, particularly in the USA and UK, in both solid organ and haematopoietic stem cell transplantation.

1.5 The Subcommittee noted that PHARMAC had recently widened funded access to ursodeoxycholic acid (UDCA) as part of conditioning therapy in stem cell or bone marrow transplant recipients to prevent veno-occlusive disease. Members noted the current Special Authority and considered that the description "hepatic complications" was more appropriate rather than veno-occlusive disease. Members **recommended** the Special Authority critieria be amended as follows:

> Initial application – (Haematological Transplant) - from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. Patient at risk of ~~veno-occlusive disease or has~~ hepatic **complications** ~~impairment~~ and is undergoing conditioning treatment prior to allogenic stem cell or bone marrow transplantation, and
> 2. Treatment for up to 13 weeks.

Exceptional Circumstances/NPPA review

1.6 The Subcommittee reviewed data provided by PHARMAC staff Exceptional Circumstances and NPPA funding applications for various transplant and immunosuppressant treatments. Members considered that in general, from the information provided, the EC/NPPA panel had approved relevant applications and declined applications where appropriate.

1.7 The Subcommittee noted that PHARMAC had recently consulted on a proposal to fund valganciclovir in the community; therefore, applications for this pharmaceutical would reduce significantly.

1.8 The Subcommittee noted the six month 450 mg daily dosing criteria proposed for valganciclovir post renal transplant. Members considered there was limited evidence for this indication and that there was an increased risk of resistance developing if this dosing schedule was funded. Members recommended that the 6 month 450 mg dosing criteria be removed.

1.9 Members considered that the proposed Special Authority criteria for valganciclovir were too complex and **recommended** the following simplified Special Authority:

> **Initial application - (transplant cytomegalovirus prophylaxis) only from a relevant specialist.** Approvals valid for 3 months where the patient has undergone a solid organ transplant and requires valganciclovir for CMV prophylaxis.
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> **Initial application - (Lung transplant cytomegalovirus prophylaxis) only from a relevant specialist.** Approvals valid for 6 months for applications meeting the following criteria:
> **Both:**
> 1. Patient has undergone a lung transplant; and
> 2. Either:
>
> 2.1 The donor was cytomegalovirus positive and the patient is cytomegalovirus negative; or
>
> 2.2 The recipient is cytomegalovirus positive.
>
> **Initial application - (Cytomegalovirus in immunocompromised patients) only from a relevant specialist**. Approvals valid for 3 months for applications meeting the following criteria:
> **Both**:
> 1. Patient is immunocompromised; and
> 2. Any of the following
>
> 2.1 Patient has cytomegalovirus syndrome or tissue invasive disease, or
> 2.2 Patient has rapidly rising plasma CMV DNA in absence of disease; or
> 2.3 Patient has cytomegalovirus retinitis
>
> Note: for the purpose of this Special Authority "immunocompromised" includes transplant recipients, patients with immunosuppressive diseases (e.g. HIV) or those receiving immunosuppressive treatment for other conditions
>
> **Renewal application - (Cytomegalovirus in immunocompromised patients) only from a relevant specialist**. Approvals valid for 3 months for applications meeting the following criteria:
> **Both**:

1. Patient is immunocompromised; and
2. Any of the following
   2.1 Patient has cytomegalovirus syndrome or tissue invasive disease, or
   2.2 Patient has rapidly rising plasma CMV DNA in absence of disease; or
   2.3 Patient has cytomegalovirus retinitis

Note: for the purpose of this Special Authority "immunocompromised" includes transplant recipients, patients with immunosuppressive diseases (e.g. HIV) or those receiving immunosuppressive treatment for other conditions

1.10 The Subcommittee questioned the preference and trend towards usage of valganciclovir compared with older oral valaciclovir, noting that randomised controlled data showed that oral valaciclovir had similar efficacy to IV ganciclovir, however, members considered that it would be very difficult to change practice as valganciclovir was now considered the standard of care.

1.11 The Subcommittee noted that funding for mycophenolate mofetil had been widened to non-transplant indications and considered that the majority of uses were now covered under the current Special Authority. Members did not consider that there was any need to further widen access to mycophenolate as recently recommended by PTAC and the Rheumatology Subcommittee.

2 Tacrolimus Brand Switch Guidelines

2.1 The Subcommittee noted a paper from PHARMAC staff regarding the outstanding 2010 Request for Proposals (RFP) for the sole supply of tacrolimus. Members noted that in May 2012 PHARMAC had written to all bidders amending the RFP parameters and that the RFP remained unresolved.

2.2 The Subcommittee noted that several suppliers had submitted dossiers for generic tacrolimus to Medsafe, however, during its review process Medsafe notified the suppliers that it would apply new EU guidelines for bioequivalence data for generic tacrolimus. Members noted that the new EU guidelines required narrower bioequivalence margins for tacrolimus, and other narrow therapeutic range drugs, of AUC(0-t) and Cmax 90% confidence intervals of 90.00 -111.11% (compared with standard bioequivalence margins of 80.00-125.00%).

2.3 The Subcommittee noted that to date only one generic tacrolimus had been approved, Tacrolimus Sandoz. [withheld under s (9(2)(i)(j)) of the OIA]

2.4 The Subcommittee noted that at its March 2010 meeting it had considered that there was no clinical reason not to award a sole supply tender for tacrolimus. However, because of pharmacokinetic variability, members considered that a brand switch for tacrolimus may require that patients undertake a clinic visit for therapeutic drug monitoring and potential dose adjustment and the Subcommittee had recommended that PTAC review bioequivalence data for relevant generic brand(s) of tacrolimus.

2.5 The Subcommittee noted that PTAC had reviewed the bioequivalence data for Tacrolimus Sandoz at its May 2010 meeting and PTAC concluded that it could be considered bioequivalent to Prograf. The Subcommittee noted, and agreed with PTACs view that inter-individual variability of blood concentrations occurs with tacrolimus, and that monitoring of patients would be important following a switch from Prograf to a generic product.

2.6 [Withheld under s (9(2)(i)(j)) of the OIA] Overall, members considered that the bioequivalence data for Tacrolimus Sandoz was more robust. Members noted that Tacrolimus Sandoz was available overseas and several hospitals overseas had already switched their transplant patients from Prograf to Tacrolimus Sandoz with no known problems.

2.7 The Subcommittee noted that they were comfortable with the Tacrolimus Sandoz product and could see no clinical reason not to award a sole supply tender to Tacrolimus Sandoz. However, the Subcommittee considered that since such a move would be a cost containment exercise only, any decision regarding implementation of a brand switch for tacrolimus needed to balance the savings to be made with the costs of the additional resources required to switch patients safely.

2.8 The Subcommittee discussed the potential resource impacts of a brand switch for tacrolimus and appropriate transition timelines and guideline requirements.

2.9 The Subcommittee considered that there were pros and cons to both long and short transition periods. On balance, the Subcommittee **recommended** a transition period of 6 months. Members considered that this would result in the additional costs associated with resources, such as patient visits or testing needed in order to manage a switch safely, being absorbed into routine clinical practice. However, members acknowledged that a long transition period increased the risks of inadvertent, unmonitored, switches occurring at the pharmacy level. Therefore, members **recommended** that patients, pharmacists and prescribers should be provided with information regarding the switch and during the transition period prescribers should prescribe by Brand.

2.10 The Subcommittee reviewed 'switching guidelines' from various overseas sources where a switch from Prograf to a generic tacrolimus had been implemented. Members noted that the level of detail differed between the various guidelines.

2.11 The Subcommittee noted that prior to any decisions being made on a brand switch PHARMAC would consult with transplant clinicians which would give sufficient notice of the timelines for any brand switch prior to it being implemented.

2.12 The Subcommittee **recommended** that PHARMAC develop high level 'brand switch' guidelines targeted at patients, clinicians prescribing tacrolimus and pharmacies dispensing tacrolimus. Members **recommended** that these guidelines include details of the brand switch, including timelines and photographs of the relevant products and that they clearly state that the switch must be managed by a transplant centre and that the patient should contact his/her transplant co-ordinator for more information.

2.13 The Subcommittee considered that in order to safely switch brands every transplant patient would need to have at least one visit to the transplant centre and would require a routine organ function assessment and three blood samples taken for tacrolimus trough

concentration analysis. Members considered that this should be sufficient for most renal, liver and cardiac transplant recipients, however, paediatric patients and lung transplant recipients may require additional visits, tests to be performed and/or blood samples taken at the discretion of the transplant centre.

2.14 The Subcommittee considered that it was not appropriate for PHARMAC to provide detailed national switch guidelines/protocols. Members considered different transplant populations may need different tests, procedures and visits to be undertaken in order to switch brands safely. Therefore, members considered that it was appropriate that each transplant centre should develop its own switching protocols based on the patient populations it serviced and its assessment of the risks and resources required to switch patients safely. The Subcommittee considered that PHARMAC high level 'brand switch' guidelines would help these centres to develop more specific guidelines for appropriate for each patient population and centre.