Transplant Immunosuppressant Subcommittee of PTAC meeting

held 4 September 2008

(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 Minutes relating to Transplant Immunosuppressant Subcommittee discussions about an application that contain a recommendation are 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.

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

- protect the privacy of natural persons (section 9(2)(a))

Contents

1 Application for the listing of Mycophenolate sodium (Myfortic) and widening of access to mycophenolate mofetil (CellCept)

1.1 The Subcommittee considered an application to list mycophenolate sodium (Myfortic) tablets, the relevant February 2008 PTAC minute and a response from a supplier to this minute. The Subcommittee further considered an application to widen access to mycophenolate mofetil (CellCept) for liver transplant and reviewed Exceptional Circumstances funding applications (EC) for mycophenolate mofetil. These items are outlined separately below.

Listing of Mycophenolate sodium (Myfortic)

1.2 The Subcommittee considered an application from Novartis New Zealand for the listing of mycophenolate sodium (Myfortic) tablets on the Pharmaceutical Schedule under the same Special Authority criteria as currently apply to mycophenolate mofetil (Cellcept, Roche Products NZ Ltd). The Subcommittee noted that the application was reviewed by PTAC at its February 2008 meeting and reviewed the relevant minute from that meeting. The Subcommittee also reviewed a letter from Roche Products NZ Ltd in response to the February 2008 PTAC minute.

1.3 The Subcommittee agreed with PTAC's view that based on data from several bioequivalence, efficacy and safety studies mycophenolate sodium (MPS) and mycophenolate mofetil (MMF) were therapeutically equivalent with comparable safety and tolerability in both de novo and maintenance renal transplant patients and that it appears to be safe to switch renal transplant patients from MMF to MPS.

1.4 The Subcommittee considered that few of the points raised in Roche Products NZ Ltd response to the February 2008 PTAC minute were valid or important to the consideration of listing MPS. The Subcommittee considered that there were some issues regarding the dosing of MPS with or without food, the pharmacokinetic differences between MPS and MMF and the range of formulations available for MPS compared with MMF; however, members considered that these issues were not directly relevant to the consideration of listing MPS and would not prevent patients successfully switching from MMF to MPS. However, members considered that in the event that MPS was listed and switching from MMF was likely to occur (eg because of reference pricing MMF), PHARMAC should provide guidance to patients, pharmacists and prescribers regarding these issues. Members further considered that it was important to continue full funding of the oral liquid formulations of MMF in the absence of an oral liquid formulation of MPS.

1.5 The Subcommittee considered that although both MPS and MMF are formulations of mycophenolic acid, there are differences in their pharmacokinetic profiles and MPS and MMF could not be considered interchangeable to avoid the possibility of switching back and forth between the products by pharmacists.

However, members noted that the risk of this happening would be very small since it was likely that if both products were listed on the Pharmaceutical Schedule they would have distinct Special Authority criteria (and therefore patients would have a specific approval number for either MPS or MMF). Most prescribers would write a prescription for either mycophenolate mofetil or mycophenolate sodium rather than simply mycophenolate, and the dosing of the two pharmaceuticals was distinct thus a pharmacist would be unable to substitute one for the other without consulting first with the prescriber.

1.6 The Subcommittee noted that MPS was only indicated for the prophylaxis of acute renal transplant rejections in adult patients receiving allogeneic renal transplants, whereas MMF was indicated for acute organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Members considered that although it was likely that MPS was therapeutically equivalent to MMF in indications other than renal transplant, they did not have sufficient evidence to recommend the listing of MPS for indications other than renal transplant at this time.

1.7 The Subcommittee considered that it was acceptable for PHARMAC to run a competitive process for the supply of mycophenolate (MPS or MMF) for adult renal transplant patients resulting in either sole supply of either MMF or MPS for these patients or reference pricing of MPS to MMF (or vice versa).

1.8 The Subcommittee **recommended** that mycophenolate sodium tablets be listed in the Pharmaceutical Schedule only for the prophylaxis of acute renal transplant rejection in adult patients only if this would provide some commercial advantage to PHARMAC.

1.9 The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Widening of access to mycophenolate mofetil (CellCept) for liver transplant recipients

1.10 The Subcommittee considered an application from [withheld under section 9(2)(a) of the OIA] requesting widening access to mycophenolate mofetil (MMF) as a calcineurin-sparing agent, to reduce the risk of renal injury in liver transplant recipients.

1.11 The Subcommittee reviewed evidence from a number of studies including data demonstrating that MMF in combination with a low dose of the calcineurin inhibitor (CNI) tacrolimus provided modest improvements in glomerular filtration rate (GFR) in patients > 1 year post liver transplant (summarised in Schemedling et al, Clinical transplantation 20 (supp 17): 75, 2006). Members noted that approximately 10% of liver transplant patients may suffer late-onset renal failure and that, in general, this was difficult to treat and would likely lead to death or the need for renal transplantation. Members considered that early declines in GFR,

secondary to CNI agents, were predictive of subsequent renal failure, and that the use of MMF as first line treatment in liver transplant patients could reduce or delay dosing of CNIs. Members were informed that currently approximately one third of patients with late-onset renal failure die, one third are re-transplanted and one third undergo successful rescue therapy.

1.12 The Subcommittee reviewed further data from two studies examining the use of MMF in combination with low dose or delayed tacrolimus for the prevention of renal dysfunction (Yoshida et al, Liver transplantation 11: 1064, 2005 and the ReSpECT study, Neuberger et al presentation at European Association for the Study of the Liver (EASL) 2008). Members noted that the manuscript for the ReSpECT study was currently being drafted. In the first study (Yoshida et al) liver transplant patients were randomised immediately following transplantation to receive either daclizumab, MMF and delayed low dose tacrolimus (4-8 ng/mL) (n=72) or MMF and normal dose tacrolimus (10-15 ng/mL) (n=76). Members noted that although there was no difference in graft or patient survival or acute rejection rates, there were significant differences in median GFR in favour of the daclizumab, MMF and delayed low dose tacrolimus arm at months one and six, but this was not maintained at one year.

1.13 The Subcommittee noted that in the ReSpECT study (Neuberger et al) 525 patients were randomised to one of three treatment groups: normal dose tacrolimus (aiming for trough blood levels of 10-15 ng/mL), low dose tacrolimus (trough levels <8 ng/mL) and MMF (1g BID), or, delayed low dose tacrolimus (trough levels <8 ng/mL after day 5), MMF (1g BID) and daclizumab. Members noted that at one year the mean decline in GFR was significantly less in both the reduced and delayed tacrolimus arms but there was no difference in graft or patient survival or acute rejection rates.

1.14 The Subcommittee considered that the evidence demonstrated that the use of MMF allowed target concentrations of tacrolimus to be reduced, with the potential to preserve renal function. Members considered that the improvements seen at one year would likely persist beyond one year and result in potential cost savings (from reduced rates of renal dialysis, renal transplantation, re-transplantation, cardiovascular morbidity and mortality associated with progression to end stage renal failure and late rejection). Members further noted that administration of MMF, with reduced tacrolimus dosing, should decrease expenditure on tacrolimus.

1.15 The Subcommittee **recommended** that funded access in the Pharmaceutical Schedule to mycophenolate mofetil be widened to include prophylaxis of renal failure in liver transplant patients and gave this recommendation a medium-to-high priority in relation to funding of other pharmaceuticals within this therapeutic area. Members considered that, if funded, transplant clinicians should use the treatment protocol used in the ReSpECT study, although their preference would be MMF (1 mg BID) and tacrolimus (dose reduced, or dose reduced and dose delayed) in combination with basiliximab rather than daclizumab.

1.16 The Subcommittee considered the decision criteria relevant to this recommendation are: (*i) the health needs of all eligible people within New Zealand; (iii) the availability and suitability of existing medicines, therapeutic*

medical devices and related products and related things; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (viii) The Government's priorities for health funding.

Widening of access to mycophenolate mofetil (CellCept) for other indications

1.17 The Subcommittee reviewed data provided by PHARMAC staff regarding Community EC and HEC funding applications for mycophenolate mofetil. Members noted that there were a large number of applications received, the majority of which were for patients post liver, lung or bone marrow transplant. There were also a number of applications for non-transplant indications for patients who had ceased responding to or no longer tolerated funded treatments, for example nephritis due to systemic lupus erythromatosis following cyclophosphamide and azathioprine, and autoimmune hepatitis following azathioprine.

1.18 Members noted that the basis of the applications was that MMF treatment would postpone dialysis and possibly organ transplantation and thus be cost-saving for DHB hospitals. Members considered that, in general, from the information provided, the EC panel had approved relevant applications and declined applications where appropriate.

1.19 The Subcommittee considered that it did not have sufficient information or evidence to recommend widening of access to MMF for any of the EC funding application indications reviewed. The Subcommittee **recommended** that applications for funding for indications outside the currently defined Special Authority criteria for MMF continue to be assessed by the EC panel; however, members suggested that PHARMAC consider including MMF on the DCS list for lupus nephritis and vascular diseases.