Scottish Medicines Consortium

mycophenolic acid (as mycophenolate sodium), 180mg and 360mg film-coated gastro-resistant tablets (Myfortic®) No. (144/04)

Novartis Pharmaceuticals UK Limited

10 December, 2004

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and ADTCs on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Mycophenolate sodium (Myfortic®) is accepted for use within NHS Scotland for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants in combination with ciclosporin and corticosteroids. It is restricted to use by transplant specialists as part of an immunosuppressive regimen.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Mycophenolic acid (as mycophenolate sodium) 180 and 360mg film-coated gastro-resistant tablets (Myfortic®)

Licensed indication under review:

In combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants. Myfortic® should be initiated and maintained by appropriately qualified transplant specialists.

Dosing information under review:

1440mg daily dose administered as 720mg twice daily.

UK launch date

6th September 2004

Comparator Medications

Azathioprine, Mycophenolate mofetil

Cost per treatment period and relevant comparators

Drug	Dose	Cost per day	Cost per year
Mycophenolic acid	**720mg twice daily**	**£8.17**	**£2980**
Mycophenolate mofetil	1g twice daily	£9.07	£3312
Azathioprine maintenance	1-4mg/kg daily (50-300mg daily)	£0.13 - £0.66	£47 - £288

Prices based on MIMS and drug tariff prices where appropriate.

Drug prices are those available at the time papers are issued to SMC for consideration.

Summary of evidence on comparative efficacy

Pharmacokinetic studies of the two mycophenolate formulations found 720mg mycophenolate sodium and 1g mycophenolate mofetil provided equivalent exposure of the active component, mycophenolic acid. The pharmacokinetics of mycophenolate sodium were linear with a T_{max} of ~2 hours, confirming delayed release compared with mycophenolate mofetil (T_{max} 0.6 hours).

Two multicentre, randomised, double-blind, parallel group, phase III studies were conducted in 745 renal transplant patients (*de novo* and maintenance). Both trials were powered to show equivalence, were for a period of 12 months and randomised patients equally to either mycophenolate sodium 720mg twice daily or mycophenolate mofetil 1g twice daily plus concomitant ciclosporin with or without corticosteroids. In the trial of 423 *de novo* patients, there was no difference in outcomes between treatments for the primary endpoint of efficacy failure, defined as a composite of the incidence of biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up within 6 months of the start of treatment, (25.8% versus 26.2%, for mycophenolate sodium (n=213) and mycophenolate mofetil (n=210) patients respectively, 95%CI (-8.7%,+8.0%)). Secondary endpoints included incidence of BPAR, graft loss or death, clinically diagnosed rejection, treated rejection, rejection requiring antibody therapy, and biopsy-proven chronic rejection (BPCR), evaluated at 6 and 12 months. There were no differences in outcomes of BPAR, graft loss or death or loss to follow up between treatment groups at 12 months (28.6% versus 28.1%, 95%CI (-8.0,+9.1), respectively).

The trial in 322 maintenance patients who were at least 6 months post transplant was to confirm if patients stabilised on mycophenolate mofetil could be converted to mycophenolate sodium without compromising safety or efficacy. The primary safety endpoints are described in the following safety section. Efficacy failure was evaluated as a secondary endpoint, measured as a composite variable of BPAR, graft loss or death at 6 and 12 months and the incidence of BPCR evaluated at 6 and 12 months. There was no significant difference between efficacy endpoints; with an efficacy failure rate of 2.5% and 6.1%, 95% CI:(-8.0%,+0.8%); BPCR of 3.8% and 4.9% and BPAR of 1.3% and 3.1% for mycophenolate sodium and mofetil patients, respectively.

Summary of evidence on comparative safety

In the two phase lll trials the incidence and profile of gastrointestinal (GI) adverse events were comparable for both treatment groups. In the *de novo* trial, the total discontinuation rates due to adverse events were 20.2% and 18.6% and the incidence of drug-related adverse events 53.1% and 60.5% for mycophenolate sodium and mofetil, respectively. Over 12 months, the number of patients experiencing GI adverse events was similar in both groups (80.8% vs 80% respectively) as was discontinuation, dose reduction or dose interruption due to GI adverse events. There was no difference between treatments in the haematological tolerability, concomitant immunosuppressive therapy, incidence of cytomegalovirus (CMV) infection or malignancy (reported in five patients from each treatment group).

In the trial of maintenance patients, the primary safety endpoints were the incidence and severity of GI adverse events at 3 months and neutropenia (defined as a low absolute neutrophil count <1500 cells/mm^3) within the first 3 months of study drug administration. Neutropenia occurred in 0.6% of mycophenolate sodium and 3.1% of mycophenolate mofetil patients, 95%CI (-6.74, +0.80) during the first three months and this remained unchanged throughout the remainder of the study. There was no significant difference between treatments in the incidence of all GI adverse events at either 3 or 6 months (26.4% vs 20.9% and 28.9% vs 27.6% for mycophenolate sodium and mofetil respectively). All secondary safety endpoints were comparable throughout the study period except for the incidence of serious infection.

In both trials, there was a difference in the reported incidence of serious infection and serious pneumonia. Results from the *de novo* patients trial showed fewer serious infections recorded for mycophenolate sodium (22.1% vs 27.1%), with the incidence of serious pneumonia significantly lower (0.5% vs 4.3%; p=0.01). In the trial of maintenance patients, although the overall incidence of infection was the same (58.5% vs 58.9% for mycophenolate sodium and mycophenolate mofetil respectively), the incidence of serious infection in the mycophenolate sodium group was significantly lower (8.8% vs 16%; p<0.05), with a non significant trend for a lower incidence of serious pneumonia (1.9% vs 4.9%;ns).

Summary of clinical effectiveness issues

For patients with end-stage renal failure, renal transplantation results in improved survival and quality of life for patients and is more cost effective than dialysis. The procedure is very successful with one-year patient survivals of 95% or above and one-year graft survival of 90% or above.

Mycophenolate mofetil is a second line treatment which is available as tablets, suspension and injection. Mycophenolate sodium is available as an enteric-coated tablet which delays release into the small intestine, where it is more soluble than in gastric fluids. However the anticipated

improvement in the GI adverse event profile due to the enteric-coating has not been proven in trials to date.

Summary of comparative health economic evidence

Based on the clinical evidence that mycophenolate sodium is at least as efficacious and safe as mycophenolate mofetil, the manufacturer shows that the cost per day is £9.07 for mycophenolate mofetil (1g twice per day) and for mycophenolate sodium the cost is £8.17 (based on 720mg twice per day).

Assuming no differences in administration of treatment and no difference in length of treatment then if the clinical evidence is accepted the economic case is proven.

Budget Impact

If all 437 patients thought to be on mycophenolate mofetil were on mycophenolate sodium the saving would be £145k per annum.

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Existing or proposed guidelines and protocols

NHS Quality Improvement Scotland have accepted and disseminated National Institute of Clinical Excellence (NICE) published Guidance (no.85) on Immunosuppressive Therapy for Renal Transplantation in Adults. It has recommended that mycophenolate mofetil is an option as part of an immunosuppressive regimen only :

- when there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or
- in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calceurin inhibitor.

Mycophenolate sodium was not included in the NICE assessment.

In August 2003 the British Transplant Society published a Consensus Statement on the use of Immunosuppression in Renal Transplantation. This states that :

- the principal aim of immunosuppressive theapy is to maximise patient and graft survival whilst optimising quality of life
- immunosuppressive protocols should be tailored to meet the specific needs of the individual patient
- to accommodate the needs of specific patients and/or patient groups and to allow individualisation of therapy, a comprehensive choice of immunosuppressive drugs is required

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 1 December, 2004.

Drug prices are those available at the time papers are issued to SMC for consideration.

References

Immunosuppressive Therapy for Renal Transplantation in Adults. Technology Appraisal Guidance 85. National Institute of Clinical Excellence. www.nice.org.uk

Bjarnason I. Enteric coating of mycophenolate sodium: a rational approach to limit topical gastrointestinal lesions and extend the therapeutic index of mycophenolate. Transplantation Proceedings 2001; 33(7-8):3238-3240.

Salvadori M, Holzer H, de Mattos A et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. American Journal of Transplantation 2004;4:231-236.

Budde K, Curtis J, Knoll G et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: Results of a 1-year study. American Journal of Transplantation 2004;4:237-243