ADIS DRUG EVALUATION

Drugs 2008; 68 (17): 2505-2533
0012-6667/08/0017-2505/$53.45/0

Enteric-Coated Mycophenolate Sodium

A Review of its Use in the Prevention of Renal Transplant Rejection

Mark Sanford and *Gillian M. Keating*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Various sections of the manuscript reviewed by:

K. Budde, Department of Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany; ***D. Cattaneo***, Department of Medicine and Transplantation, Ospedali Riuniti di Bergamo and Mario Negri Institute for Pharmacological Research, Bergamo, Italy; ***N. Kamar***, Department of Nephrology-Transplantation, Hôpital Rangueil, Toulouse, France; ***L. Pape***, Department of Pediatric Nephrology, Medical School of Hannover, Hannover, Germany; ***A.L. Serra***, Department of Nephrology, University Hospital, Clinic for Nephrology, Zurich, Switzerland; ***M. Shipkova***, Central Institute of Clinical Chemistry and Laboratory Medicine, Klinikum Stuttgart, Stuttgart, Germany.

Data Selection

Sources: Medical literature published in any language since 1980 on 'mycophenolate sodium delayed-release', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'mycophenolate sodium' and ('renal or kidney transplant' and 'rejection'). Searches were last updated 13 November 2008.

Selection: Studies in renal transplant patients who received mycophenolate sodium delayed-release for the prevention of renal graft rejection. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Mycophenolate sodium, renal transplant rejection, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Enteric-coated mycophenolate sodium (Myfortic®) is a reversible, noncompetitive inosine monophosphate dehydrogenase (IMPDH) inhibitor that is approved in the EU, the US and in other countries worldwide for immunosuppressive prophylaxis against graft rejection in adult renal transplant patients.

Enteric-coated mycophenolate sodium has a delayed absorption from the gastrointestinal (GI) tract in comparison with mycophenolate mofetil, thereby potentially reducing GI adverse events. In randomized, double-blind trials of *de novo* and maintenance immunosuppressive therapy in renal transplant patients receiving ciclosporin emulsion-based regimens, enteric-coated mycophenolate sodium was as effective as mycophenolate mofetil in preventing renal graft rejection. Enteric-coated mycophenolate sodium provides an alternative to mycophenolate mofetil in the treatment of *de novo* renal transplant recipients and ongoing research should indicate whether an intensified dosage regimen can further improve clinical outcomes. Renal transplant patients receiving mycophenolate mofetil maintenance immunosuppressive therapy may be switched to enteric-coated mycophenolate sodium without compromising efficacy.

The general tolerability profile of enteric-coated mycophenolate sodium was similar to that of mycophenolate mofetil. Patients selected for GI intolerance associated with mycophenolate mofetil treatment showed reductions in GI symptoms when switched to enteric-coated mycophenolate sodium, while in unselected patients in comparative trials, there was no difference between enteric-coated mycophenolate sodium and mycophenolate mofetil in GI tolerability. Enteric-coated mycophenolate sodium provides an alternative to mycophenolate mofetil in renal transplant patients receiving mycophenolate mofetil maintenance immunosuppressive therapy who have GI symptoms that have not responded to other management strategies, because they may experience improvement if switched to enteric-coated mycophenolate sodium. Thus, in association with ciclosporin-based regimens, enteric-coated mycophenolate sodium is a valuable treatment option for immunosuppressive prophylaxis in adult renal transplant recipients.

Pharmacological Properties

In stable renal transplant patients, the inhibitory effect of enteric-coated mycophenolate sodium on IMPDH, T-cell proliferation, T-cell activation, lymphocyte subsets and cytokine expression was not significantly different from that of mycophenolate mofetil.

Mycophenolic acid (MPA) is released from enteric-coated mycophenolate sodium in the small intestine. In renal transplant patients receiving maintenance immunosuppressive therapy, the exposure to MPA with enteric-coated mycophenolate sodium treatment was equivalent to that seen with mycophenolate mofetil treatment, although the time to maximum plasma concentration was longer, as expected with an enteric-coated formulation. As observed with mycophenolate mofetil, in *de novo* renal transplant recipients, MPA exposure with enteric-coated mycophenolate sodium was generally lower in the immediate post-transplant period than in the maintenance period, although an intensified dosage regimen early after transplantation increased exposure to MPA. There is considerable interindividual and intraindividual variability in MPA pharmacokinetics with enteric-coated mycophenolate sodium and mycophenolate mofetil. In paediatric patients, MPA exposure with a single dose of enteric-coated mycophenolate sodium was slightly higher than that observed in adult patients.

Therapeutic Efficacy

In randomized, double-blind, double-dummy, multinational trials, at recommended dosages, enteric-coated mycophenolate sodium had equivalent efficacy to mycophenolate mofetil in *de novo* renal transplant recipients, and renal transplant patients receiving maintenance immunosuppressive therapy could be switched from mycophenolate mofetil to enteric-coated mycophenolate sodium without affecting efficacy. Extension studies demonstrated that the efficacy of mycophenolate sodium was maintained in the longer term. Large, prospective, noncomparative studies confirm that *de novo* renal transplant recipients can be effectively treated with enteric-coated mycophenolate sodium, with low rates of renal graft loss and the establishment of stable renal functioning; renal transplant patients receiving maintenance immunosuppressive therapy switched from mycophenolate mofetil to enteric-coated mycophenolate sodium had low treatment failure rates, with no patient experiencing graft loss, and continuing stable renal function.

Tolerability

In randomized, double-blind, multinational trials in *de novo* renal transplant patients and renal transplant patients receiving maintenance immunosuppressive therapy, the most common adverse events associated with mycophenolate sodium treatment were infections and GI symptoms. There were no significant differences between enteric-coated mycophenolate sodium and mycophenolate mofetil treatment groups in the incidence of general or serious adverse events, except that enteric-coated mycophenolate sodium recipients had a lower rate of serious pneumonia in *de novo* renal transplant patients and serious infections in renal transplant patients receiving maintenance immunosuppressive therapy.

The GI tolerability of enteric-coated mycophenolate sodium was no different to that of mycophenolate mofetil in *de novo* and renal transplant patients receiving maintenance immunosuppressive therapy in randomized, double-blind, multinational trials. In PROGIS and myTIME studies, in patients who had received renal transplants ≥1 month previously and who were experiencing GI symptoms while receiving mycophenolate mofetil, switching to enteric-coated mycophenolate sodium was associated with a significant reduction in GI symptom scores and an improvement in GI health-related quality of life.

1. Introduction

Renal transplantation is an effective treatment for end-stage renal disease.[1] In the US, more than 16 000 transplants were performed in 2007,[2] the majority being allograft organs from deceased donors.[2] Following surgery, treatment is aimed at preventing graft failure.

Antibody- and cellular-mediated mechanisms are the immediate causes of renal graft failure.[3] These acute immunological events and the resulting endothelial damage set in train reparative processes that contribute to chronic graft rejection,[3] although it is worth bearing in mind that non-immunological factors causing endothelial damage are also important, including cold ischaemia, infections, hyperlipidaemia, hypertension and other haemodynamic factors.[4]

Prophylactic immunosuppressive treatments are initiated immediately following transplantation and are targeted to inhibit proliferation of T and B cells.[1,5] It is essential that early effective immunosuppression is achieved and maintained, as this leads to better graft survival.[1] However, despite improvements in treatment over recent decades, 4% of renal grafts fail annually.[5] Therefore, new efficacious, better tolerated drug regimens that can be used without interruption are needed.[1]

Standard immunosuppressive regimens include calcineurin inhibitors (such as ciclosporin or tacrolimus), corticosteroids and mycophenolic acid (MPA),[6] along with induction therapies that may include monoclonal and polyclonal antibodies, intravenous immunoglobulins and plasmapheresis.[7] MPA is a well established immunosuppressive drug that has been used in renal transplant prophylaxis over the last two decades.[6] The first oral preparation of MPA was an ester prodrug, mycophenolate mofetil, which is rapidly absorbed and de-esterified to MPA.[8] The most common adverse events in mycophenolate mofetil recipients include gastrointestinal (GI) and haematological adverse events,[6,9] which can lead to dose reductions or interruptions that may be associated with an increased risk of graft rejection.[10,11]

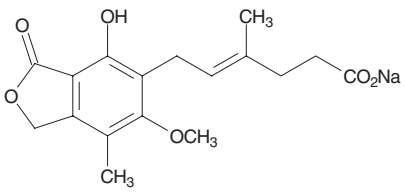

Fig. 1. Chemical structure of mycophenolate sodium

Enteric-coated mycophenolate sodium (Myfortic®)[1] [figure 1] is an enteric-coated formulation of MPA developed with the aim of minimizing upper GI effects related to MPA by passing the drug through the stomach before its release and absorption.[12,13] It is approved in the EU,[14] the US[15] and other countries worldwide for use with ciclosporin and corticosteroids in adult patients for the prevention of graft rejection following renal transplantation. This article focuses on the pharmacology, clinical efficacy and tolerability of enteric-coated mycophenolate sodium when used within this indication. Enteric-coated mycophenolate sodium has also been used in heart and liver transplantation[16-18] and in various immune disorders,[19-21] but discussion of its use in these populations is outside the scope of this review.

2. Pharmacodynamic Properties

Enteric-coated mycophenolate sodium dissolves in aqueous media at physiological pH to release MPA, which inhibits DNA synthesis and the proliferation of T and B cells.[9,15] MPA is a potent, reversible, noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH),[12] which catalyses the oxidation of inosine 5′-monophosphate to xanthosine 5′-monophosphate, along with the reduction of nicotinamide adenine dinucleotide.[22] This is the initial rate-limiting step in the *de novo* production of guanosine nucleotides, which are essential for cell proliferation.[12] The binding affinity of MPA is high for the IMPDH type II isoenzyme that is predominant in proliferating lymphocytes.[9,12] As a result, MPA has a cytostatic effect on

1 The use of trade names is for identification purposes only and does not imply endorsement.

T and B cells, as both require guanosine triphosphate for *de novo* synthesis of guanosine nucleotides, whereas other cell types can recycle purine bases using alternative salvage pathways.[9,12,23]

The immunosuppressive effect of enteric-coated mycophenolate sodium depends on the inhibitory effect of MPA on IMPDH.[12] In a substudy[24] of a large, randomized, double-blind trial[25] in stable renal transplant patients receiving maintenance immunosuppressive therapy (n = 18) [see sections 4 and 5], enteric-coated mycophenolate sodium 720 mg twice daily and mycophenolate mofetil 1000 mg twice daily had a similar inhibitory effect on IMPDH, with mean maximum enzyme inhibition values of 84% and 85% and mean concentrations causing 50% inhibition of 4.2 and 3.6 μg/mL. As might be expected for an enteric-coated formulation, the median time to reach minimum IMPDH activity was longer for enteric-coated mycophenolate sodium than mycophenolate mofetil (1.5 vs 1.0 hours; $p < 0.05$).[24] Maximum plasma MPA concentration (C_{max}) values of >10–15 μg/mL can be expected to lead to a marked inhibition of IMPDH activity[24] and these concentrations are well exceeded with standard dosage protocols (section 3).

Intensified treatment with enteric-coated mycophenolate sodium early after transplantation produced a higher level of IMPDH inhibition than standard dosages.[26] In a randomized trial in *de novo* renal transplant recipients (n = 75) receiving ciclosporin-based regimens, intensified treatment with enteric-coated mycophenolate sodium 2880 mg/day on days 1–14, 2160 mg/day on days 15–42 and 1440 mg/day on days 43–180 resulted in a lower IMPDH-area effect curve than the standard enteric-coated mycophenolate sodium regimen (1440 mg/day from day 1) [33.2 vs 45.1 (nmol/mg protein • h) • h; $p = 0.03$].[26]

The main immunosuppressive effect of MPA is thought to be related to the inhibition of proliferative responses of T and B cells to mitogenic and allospecific stimulation.[23] However, MPA also suppresses B-cell antibody formation and inhibits the production of the lymphocyte and monocyte glycoproteins that are important to the adherence of inflammatory cells to allograft endothelial cells.[23] These mechanisms are thought to be important in preventing the inflammatory processes that cause renal vessel atherosclerosis, interstitial fibrosis, glomerulosclerosis, tubular atrophy and deteriorating renal function, which are the hallmarks of chronic graft rejection.[4] In animal studies, enteric-coated mycophenolate sodium prevented intimal thickening and other histological changes that accompany graft rejection, as well as reducing antibody production.[13]

There was no reduction in pharmacodynamic effects after switching renal transplant patients receiving maintenance immunosuppressive therapy from mycophenolate mofetil to enteric-coated mycophenolate sodium.[27] In tacrolimus-treated patients with stable renal function (n = 10) switched from mycophenolate mofetil 500 mg twice daily to enteric-coated mycophenolate sodium 360 mg twice daily, there were no significant differences between baseline and 1- to 6-month follow-up measurements of T-cell proliferation, T-lymphocyte activation, lymphocyte subpopulations or in interleukin-2 and tumour necrosis factor-α expression in CD3+ T cells.[27]

In the US, patients with diabetes mellitus make up ≈50% of renal transplants recipients and it is important to know whether the effects of enteric-coated mycophenolate sodium are similar in this subpopulation to those of the non-diabetic renal transplant population.[28] In an open-label study in stable renal transplant patients with or without diabetes (n = 18) treated with enteric-coated mycophenolate sodium, IMPDH activity was lower in diabetic (mean dosage 960 mg/day) than in non-diabetic patients (mean dosage 1120 mg/day) throughout the 12-hour drug administration interval ($p < 0.0001$).[28] The greatest IMPDH inhibition occurred 2 hours after administration of enteric-coated mycophenolate sodium, at which time IMPDH inhibition was 3-fold greater in diabetic than in non-diabetic patients ($p = 0.012$). This was despite non-diabetic patients receiving a higher enteric-coated mycophenolate sodium dosage and an equivalent MPA exposure. The causes and exact

clinical implications of these findings are unknown.[28]

The chief rationale for developing an enteric-coated formulation of MPA was to reduce upper GI adverse effects by eliminating local exposure to MPA or its metabolites in the stomach.[10,12] A possible cause of toxicity is the proinflammatory metabolite acyl MPA glucuronide (acylMPAG) [section 3], which inhibits IMPDH[29] and may be produced by intestinal cells and released into the gut lumen.[10] Alternatively, systemic acylMPAG may induce GI symptoms, although, in renal transplant patients there was no indication of an increase in plasma acylMPAG concentrations before episodes of diarrhoea.[30] GI symptoms were more frequent when mycophenolate mofetil was administered with tacrolimus than with ciclosporin.[30] A possible explanation is that because tacrolimus is not associated with enterohepatic recycling of MPA, it results in higher biliary excretion of MPA glucuronide (MPAG) and acylMPAG than ciclosporin, leading to an increased likelihood of lower GI tract irritation.[30] However, this remains speculative, as it is unknown whether acylMPAG has GI toxic effects or whether it is available locally in sufficient quantities to produce irritation.[10]

During treatment with MPA, vaccinations may be less effective and the use of live vaccines should be avoided.[14,15]

3. Pharmacokinetic Properties

This section reviews the pharmacokinetics of enteric-coated mycophenolate sodium. Two trials investigated the bioequivalence between single-[31] or multiple-dose[24] enteric-coated mycophenolate sodium and mycophenolate mofetil in renal transplant patients receiving maintenance immunosuppressive therapy. For the purposes of these studies, bioequivalence was established between enteric-coated mycophenolate sodium and mycophenolate mofetil if the 90% confidence interval (CI) of the enteric-coated mycophenolate sodium : mycophenolate mofetil ratios for the area under the plasma concentration-time curve (AUC) and C_{max} were within prespecified limits (90% CI 0.80, 1.25).[24,31] A crossover study in renal transplant patients receiving maintenance immunosuppressive therapy provides additional MPA steady-state pharmacokinetic data for enteric-coated mycophenolate sodium, including data on its relative abundance after the administration of enteric-coated mycophenolate sodium or mycophenolate mofetil.[32] Another study compared the pharmacokinetic properties of enteric-coated mycophenolate sodium in intensified- versus standard-dosage regimens early after transplantation.[26] With enteric-coated mycophenolate sodium, MPA exposure has been shown to be dose proportional over the dose range of 180–2160 mg;[33] this section will focus on the pharmacokinetics of the approved dosage of 720 mg twice daily. Some studies are only available as abstracts.[26,34-36] In the absence of studies of therapeutic drug monitoring with enteric-coated mycophenolate sodium, the discussion of therapeutic drug monitoring (section 3.5) reports data from patients treated with mycophenolate mofetil.

3.1 Absorption and Distribution

Enteric-coated mycophenolate sodium is the enteric-coated sodium salt of MPA.[14,15] It has low solubility in acidic media and high solubility at pH >5.5–6.0,[31] along with high intestinal permeability.[33] *In vitro* dissolution studies showed no release of MPA from enteric-coated mycophenolate sodium at a pH of 1 (i.e. stomach pH), while there was maximal release of MPA at a pH of 6.0 or 6.8 and slightly delayed release at a pH of 5.5 (these pH values reflect intestinal pH).[31] Only partial MPA release (≤40% of the dose) was seen at a pH of 5.0.[31]

The absorption pharmacokinetics of single-[31,37] and multiple-dose[14,24] enteric-coated mycophenolate sodium in adult *de novo* renal transplant recipients,[14] adult patients receiving maintenance immunosuppressive therapy[24,31,32] and paediatric[37] renal transplant patients aged ≥5 years also receiving ciclosporin emulsion-based regimens are summarized in table I. Oral enteric-coated mycophenolate sodium had a mean absolute bioavailability of 71% in stable renal transplant patients receiving maintenance immunosuppressive therapy.[33]

Table I. Pharmacokinetics of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant patients. Mean values unless stated otherwise

Study [design details]	Treatment [no. of patients]	Timepoint	MPA t_{max}[a] (h)	MPA C_{max} (μg/mL)	MPA AUC (μg • h/mL)
In *de novo* renal transplant patients					
Study ERL B301[14] [r, db][b]	EC-MPS 720 mg bid [48]	14 d post-transplant	2	13.9	29.1[c]
	EC-MPS 720 mg bid [48]	3 mo post-transplant	2	24.6	50.7[c]
In stable maintenance treatment renal transplant patients					
Arns et al.[31] [r, ol, co]	EC-MPS 640 mg [24]	SD	2.0**	30.1	60.7[d]
	EC-MPS 720 mg	SD	2.0**	26.1	66.5[d]
	MMF 1000 mg	SD	0.75	30.2	63.7[d]
Budde et al.[24] [r, db][b]	EC-MPS 720 mg bid [9]	15 mo	1.5*	18.9	57.4[c]
	MMF 1000 mg bid [9]	Baseline	0.8	21.3	58.4[c]
Tedesco-Silva et al.[32] [ol, co]	EC-MPS 720 mg bid [40]	≥3 mo	2.5[e]	33.4	74.7[c]
	MMF 1000 mg bid	≥3 mo	1.0	25.5	61.4[c]
In paediatric renal transplant patients aged ≥5 years					
Ettenger et al.[37] [nc]	EC-MPS 360–720 mg [25]	SD	2.5	36.3	74.3[d]

a Median values.

b Substudy of pivotal trials in *de novo*[41] and maintenance treatment[25] renal transplant patients.

c Steady-state AUC from time 0 to 12 h.

d AUC from time zero to infinity.

e No statistical analysis used to test vs MMF.

AUC = area under the plasma concentration-time curve; **bid** = twice daily; **co** = crossover; **C_{max}** = maximum plasma concentration; **db** = double-blind; **MMF** = mycophenolate mofetil; **MPA** = mycophenolic acid; **nc** = noncomparative; **ol** = open-label; **r** = randomized; **SD** = single dose; **t_{max}** = time to C_{max}; * $p < 0.05$, ** $p < 0.01$ vs MMF.

Oral administration of single doses of enteric-coated mycophenolate sodium and mycophenolate mofetil led to equivalent MPA exposure in stable renal transplant patients receiving ciclosporin-based maintenance immunosuppression.[31] In terms of the AUC ratio, bioequivalence with mycophenolate mofetil 1000 mg was seen for both enteric-coated mycophenolate sodium 640 mg (90% CI 0.87, 1.04) and 720 mg (90% CI 0.91, 1.09). However, the two formulations were not bioequivalent for C_{max} ratios (90% CI 0.71, 1.40 for enteric-coated mycophenolate sodium 640 mg and 90% CI 0.57, 1.12 for enteric-coated mycophenolate sodium 720 mg), presumably because of high interpatient variability.[31] The absorption of enteric-coated mycophenolate sodium was significantly slower than that of mycophenolate mofetil; the median time to reach C_{max} (t_{max}) was more than doubled (table I).[31] After reaching C_{max}, there was a gradual fall in the MPA concentration over ≈6 hours, with a second peak in some patients between 6 and 12 hours.[31] This is consistent with studies of mycophenolate mofetil combined with ciclosporin that show that enterohepatic recycling of MPA led to a second peak in plasma concentrations after 4–12 hours.[38] There is indirect evidence that tacrolimus is not associated with enterohepatic recycling.[30]

In multiple-dose studies in renal transplant recipients receiving maintenance immunosuppressive therapy, enteric-coated mycophenolate sodium 720 mg twice daily was bioequivalent to mycophenolate mofetil 1000 mg twice daily in terms of the steady-state MPA AUC ratio (90% CI 0.87, 1.11[24] and 90% CI 1.04, 1.25[32]) [table I]. As expected, the median t_{max} for MPA was longer for enteric-coated mycophenolate sodium than for mycophenolate mofetil (table I).[24,32] In the double-blind study, the lower limit of the 90% CI for the C_{max} geometric mean ratio fell outside the bioequivalence range (90% CI 0.70, 1.13).[24] Mean predose MPA concen-

trations were 4.35 μg/mL with enteric-coated mycophenolate sodium and 1.80 μg/mL with mycophenolate mofetil (geometric mean ratio 1.34; 90% CI 1.13, 1.59), reflecting the delayed release of MPA that occurs with the enteric-coated formulation.[24]

Consistent with findings in patients receiving mycophenolate mofetil,[8] exposure to MPA was lower on day 14 in newly transplanted patients receiving enteric-coated mycophenolate sodium 720 mg twice daily than at 3 months (table I).[14] Similarly, when enteric-coated mycophenolate sodium 720 mg was administered twice daily to renal transplant patients treated with ciclosporin and corticosteroids (n = 17), only nine patients achieved the expected MPA exposure (AUC from time 0 to 12 hours [AUC_{12}] 30–60 μg • h/mL) early after transplantation; the overall median MPA AUC_{12} was 26.0 μg • h/mL.[34] In contrast, one study reported adequate early exposure with enteric-coated mycophenolate sodium in Thai *de novo* renal transplant recipients treated with ciclosporin microemulsion and corticosteroids (n = 12) [mean MPA AUC_{12} of 73.9 μg • h/mL on day 1 and 74.3 μg • h/mL on day 14].[39] In this study, 10 of 12 patients were recipients of grafts from living donors and the mean body weight was 48.1 kg, factors which may account for the discrepant findings.[39]

A substudy (n = 48)[40] of a randomized trial in *de novo* renal transplant recipients (section 4),[41] provides longer-term comparative pharmacokinetic data for mycophenolate sodium and mycophenolate mofetil; this study has not been published in full and statistical analyses are not fully reported, so the findings should be considered preliminary. Enteric-coated mycophenolate sodium 720 mg twice daily was associated with a 32% increase in MPA exposure over a 6-month treatment period relative to mycophenolate mofetil 1000 mg twice daily ($p = 0.004$); mean AUCs at 14, 90 and 180 days were 29.1, 50.7 and 55.7 μg • h/mL, respectively, in enteric-coated mycophenolate sodium recipients, and 23.3, 39.1 and 37.2 μg • h/mL in mycophenolate mofetil recipients. The proportion of patients with an AUC >30 μg • h/mL at 14, 90 and 180 days were 55%, 86% and 100%, respectively, with enteric-coated mycophenolate sodium (vs 15%, 76% and 72% with mycophenolate mofetil) [statistical analysis not reported].[40]

An intensified dosage regimen during the early post-transplant period led to a higher MPA exposure and this approach may contribute to better outcomes.[26] In the intensified dosage regimen study (see section 2 for dosage and design details), in comparison with standard dosages, an intensified dosage regimen led to higher MPA exposure (AUC 44.9 vs 31.8 μg • h/mL; $p = 0.022$) and free MPA exposure (AUC 2.242 vs 1.162 μg • h/mL; $p = 0.002$) on day 3 after transplantation.[26] During the following 3 months, MPA exposure remained stable despite the reducing dosages of enteric-coated mycophenolate sodium.[26]

When enteric-coated mycophenolate sodium was administered with a high-fat meal, there was no change in overall systemic exposure to MPA, although the C_{max} was reduced by 33% and the rate of absorption was slowed (t_{max} was delayed on average by 5 hours).[14] Although this effect was not thought to be clinically important,[14] in the US,[15] patients are recommended to take enteric-coated mycophenolate sodium 1 hour before or 2 hours after food intake; in the EU, patients are asked to select administration with or without food and then to adhere to their selection.[14]

High interindividual and intraindividual variability in MPA concentrations, especially trough concentrations,[24,42] has been observed after oral enteric-coated mycophenolate sodium or mycophenolate mofetil administration.[8,24,31,38,42] For instance, in a multiple-dose study, the coefficient of variability was ≤43% for all pharmacokinetic parameters for both MPA formulations, except for MPA trough concentration (82% and 42% for enteric-coated mycophenolate sodium and mycophenolate mofetil).[24] In renal transplant patients evaluated 6 months after surgery, dosage-normalized MPA trough concentrations were 3.6-fold higher in enteric-coated mycophenolate sodium (n =12) than mycophenolate mofetil (n = 20) recipients, with significantly ($p < 0.05$) higher interpatient variability in enteric-coated mycophenolate sodium than mycophenolate

mofetil recipients at three out of four timepoints (at all four assessments, variability in trough MPA concentration was >80% for enteric-coated mycophenolate sodium and between 47% and 60% for mycophenolate mofetil).[42] Compared with mycophenolate mofetil, interpatient variability with enteric-coated mycophenolate sodium was higher for MPA t_{max} at 12 and 18 months (not at 6 and 24 months), as was intrapatient variability in MPA t_{max} and AUC_{12}.[42]

At steady state, the volume of distribution of MPA is 54 L and it is highly bound to plasma proteins (>98% to albumin).[15]

3.2 Metabolism and Elimination

Following the release of MPA from enteric-coated mycophenolate sodium in the small intestine,[24] it is absorbed and metabolized primarily in the liver by glucuronyl transferase to form the pharmacologically inactive metabolite MPAG.[14,15] AcylMPAG and a glucoside conjugate of MPA have also been detected.[29] AcylMPAG has pharmacological activity and contributes ≈14% of the exposure to the active drug.[32] In a crossover study in renal transplant patients (n = 40), the acylMPAG mean C_{max} and mean AUC_{12} values were 4.1 and 3.9 μg/mL and 19.6 and 18.8 μg • h/mL, respectively, for enteric-coated mycophenolate sodium 720 mg/day and mycophenolate mofetil 1000 mg/day after 28 days of treatment. Point estimates for acylMPAG C_{max} and AUC_{12} indicated that, with respect to exposure to acylMPAG, mycophenolate sodium was equivalent to mycophenolate mofetil.[32]

MPA is eliminated primarily via the kidneys.[15] After a radiolabelled oral dose of enteric-coated mycophenolate sodium, >60% of the radioactivity was recovered as MPAG and ≈3% as the active drug. The mean renal clearance was 140 mL/min for MPA and 15.5 mL/min for MPAG.[15] Some MPAG was secreted in bile and reabsorbed into the systemic circulation as MPA after being deconjugated by gut flora, at times producing a second peak in MPA concentration ≈6–8 hours after the initial dose. The mean elimination half-life ($t_{½\beta}$) of MPA was 8–16 hours ($t_{½\beta}$ of MPAG was 13–17 hours), indicating that twice-daily administration should ensure adequate exposure to the drug.[15]

3.3 Special Populations

The pharmacokinetics of a single dose of enteric-coated mycophenolate sodium (≈450 mg/m^2) in paediatric renal transplant recipients (aged 5–16 years) were broadly similar to those seen in adults (table I).[37] Patients were receiving a ciclosporin microemulsion-based regimen; mycophenolate mofetil treatment was withdrawn 48 hours before treatment with enteric-coated mycophenolate sodium. After enteric-coated mycophenolate sodium, children aged 5–10 years (n = 12) had a higher MPA exposure than children aged 11–16 years (n = 13) [C_{max} 40.2 vs 33.0 μg/mL and AUC from time zero to infinity (AUC_{∞}) 82.2 vs 66.4 μg • h/mL]. The higher exposure to MPA, especially in younger children, probably occurred because the children were dosed on the basis of body surface area (BSA).[37] Although the higher exposure is not considered to be clinically important, lower doses based on bodyweight can be used (see section 6 for paediatric dosage recommendations[15]).

There are limited data on the pharmacokinetics of enteric-coated mycophenolate sodium in patients with renal or hepatic impairment.[15] However, in studies in patients with renal impairment receiving mycophenolate mofetil, MPA concentrations were not appreciably increased.[15] The US prescribing information for enteric-coated mycophenolate sodium indicates that no dosage adjustments are required for patients with delayed graft functioning following transplantation, but that patients with severe chronic renal impairment should be monitored closely for adverse effects. In patients with hepatic cirrhosis, MPA pharmacokinetics after administration of mycophenolate mofetil were relatively unaffected.[15] In the US, no dosage adjustments are necessary in patients with hepatic impairment.[14,15]

Enteric-coated mycophenolate sodium pharmacokinetics were not significantly different when renal transplant patients with diabetes were compared with non-diabetic transplant recipients.[28]

3.4 Potential Drug Interactions

Drug interactions may occur when enteric-coated mycophenolate sodium is coadministered with antacids, cholestyramine, oral contraceptives, antiviral agents and other immunosuppressive drugs.[14,15] A single dose of magnesium/aluminium-containing antacids administered with enteric-coated mycophenolate sodium reduced MPA exposure by ≈37%. It is recommended that while antacids may be used intermittently, they should not be used long-term on a daily basis,[14] or administered simultaneously with enteric-coated mycophenolate sodium.[15] In addition, coadministration of mycophenolate mofetil with cholestyramine and other bile-acid-binding agents was found to reduce enterohepatic recycling of MPA. The same interaction could be expected with enteric-coated mycophenolate sodium; therefore, it is recommended that enteric-coated mycophenolate sodium is not coadministered with bile acid-binding agents.[15] Drugs that reduce gut flora could disrupt enterohepatic recycling, but there are no specific recommendations regarding their coadministration with enteric-coated mycophenolate sodium.[15]

Mycophenolate mofetil coadministered with the oral contraceptive levonorgestrel reduced levonorgestrel exposure by 15%.[15] Therefore, it is recommended that consideration should be given to using additional birth control methods when oral contraceptives are coadministered with enteric-coated mycophenolate sodium.[15]

The proton-pump inhibitor (PPI) lansoprazole, when coadministered with mycophenolate mofetil and tacrolimus, lowered MPA exposure, an effect that was associated with multidrug resistance polymorphisms.[43] The PPI rabeprazole was not associated with lower MPA concentrations, suggesting that this effect was specific to lansoprazole, perhaps because of its inhibitory effect on gastric acid secretion.[43] There are no data regarding coadministration of enteric-coated mycophenolate sodium with other PPIs.

Aciclovir and ganciclovir could increase exposure to plasma MPAG or to the antiviral agent through competition for renal tubular secretion.[14,15] Monitoring of blood cell counts is recommended for patients taking these antivirals with enteric-coated mycophenolate sodium.[15]

At steady state, enteric-coated mycophenolate sodium is reported to not affect the pharmacokinetics of ciclosporin.[14,15] However, 6 months after transplantation in recipients of deceased donor renal transplants (n =12), mean plasma ciclosporin concentrations at 2 and 3 hours after drug administration were higher in patients receiving enteric-coated mycophenolate sodium than in matched controls receiving mycophenolate mofetil (n = 20), and t_{max} was longer (1.9 vs 1.5 hours; p = 0.04) [these specific concentration and t_{max} differences were also present at 12, 18 and 24 months after transplantation].[44] The clinical significance of these findings remains to be explored, but may be relevant if clinicians are using 2-hour post-dose ciclosporin blood monitoring to determine ciclosporin dosage. Ciclosporin appears to inhibit excretion of MPAG in the bile, reducing enterohepatic recycling of MPA.[45] Thus, concomitant administration of enteric-coated mycophenolate sodium and ciclosporin may reduce MPA exposure.[14] If ciclosporin is interrupted or discontinued, the enteric-coated mycophenolate sodium dosage may need to be re-evaluated.[14]

Tacrolimus does not appear to inhibit the enterohepatic recycling of MPA, meaning that patients receiving enteric-coated mycophenolate sodium and tacrolimus could potentially have higher MPA exposure than those receiving enteric-coated mycophenolate sodium and ciclosporin.[45] However, MPA exposure was not increased to a significant extent in patients receiving enteric-coated mycophenolate sodium who were switched from ciclosporin microemulsion to tacrolimus.[46] In patients treated with mycophenolate mofetil, diarrhoea was more frequent in those receiving tacrolimus than ciclosporin regimens, but exposure to MPA or its metabolites in the first 3 months of treatment was not different in those with or without diarrhoea, suggesting that another mechanism is at play.[30] In stable renal transplant patients receiving tacrolimus who were switched from mycophenolate mofetil to

enteric-coated mycophenolate sodium, tacrolimus C_{max} and AUC values were 20% and 18% lower after the switch ($p = 0.0013$) and the MPA AUC was 27% higher after the switch (statistical analyses not reported).[47] These differences were considered to be of no clinical significance.[47] From a clinical standpoint, there is no indication that dosage adjustments are necessary when coadministering enteric-coated mycophenolate sodium with tacrolimus.

Switching from tacrolimus to everolimus also did not alter the pharmacokinetics of enteric-coated mycophenolate sodium.[35] In contrast, switching from ciclosporin to everolimus led to a 55% higher exposure to MPA (mean MPA AUC was 27.9 μg • h/mL when the ciclosporin dosage was at 100% of baseline, 33.9 μg • h/mL at ciclosporin 50% and 43.3 μg • h/mL when ciclosporin was completely withdrawn).[36] These higher MPA concentrations led to a 59% reduction in IMPDH activity ($p < 0.005$) and close monitoring of MPA pharmacokinetics was suggested when using enteric-coated mycophenolate sodium with everolimus.[36]

It is recommended that enteric-coated mycophenolate sodium is not coadministered with azathioprine, as both drugs lead to inhibition of purine metabolism,[15] which would increase the risk of myelosuppression.

3.5 Therapeutic Drug Monitoring

Systemic exposure to free MPA is presumed to be responsible for its immunosuppressive effect.[8,38] Based on studies of mycophenolate mofetil in combination with ciclosporin, a MPA AUC_{12} of 30–60 μg • h/mL is suggested as providing adequate immunosuppression and a lower risk of adverse events in the early post-transplantation period, although in most studies there is no relationship between adverse events and MPA exposure.[38,48,49] Lower acute rejection rates with adequate MPA exposure, interindividual variability in MPA pharmacokinetics and lower drug exposure early after transplantation suggest that therapeutic drug monitoring may provide better prophylaxis against graft failure than using fixed dosages.[48,50]

However, currently, there is uncertainty as to the value of therapeutic drug monitoring for MPA in this clinical population.[49,51] One of the obstacles is the lack of a relationship between MPA trough concentrations, which are convenient to measure, and the AUC.[49] The first published trial of therapeutic drug monitoring evaluated a fixed dose of mycophenolate mofetil 1000 mg twice daily versus dosage adjustment of mycophenolate mofetil based on a targeted MPA AUC of 40 μg • h/mL (AUC derived from a Bayesian estimator from samples taken 20, 60 and 180 minutes after drug administration on days 7 and 14, and months 1, 3, 6 and 12).[52] Patients were randomized within 3 days of renal transplantation (n = 65) and followed-up for 12 months. The AUC-targeted group received a higher daily dosage of mycophenolate mofetil ($p < 0.0001$) and experienced fewer treatment failures (29.2% vs 47.7%; $p = 0.03$) and biopsy-proven acute rejection episodes (7.7% vs 24.6%; $p = 0.01$) than the fixed dose group.[52] A recent randomized, 12-month trial in paediatric and adult renal transplant recipients aged ≥2 years (n = 901; 62 patients were aged <18 years) evaluated clinical outcomes with fixed-dose versus concentration-controlled mycophenolate mofetil treatment.[53] The dosage in the concentration-controlled treatment group was based on an abbreviated AUC_{12} derived from three MPA concentrations taken predose, 30 and 120 minutes after drug administration on days 3 and 10, week 4, and months 3, 6 and 12 after transplantation. There were no significant differences between the two treatment groups in treatment failure or biopsy-proven acute rejection. However, this finding may, in part, be related to the fact that, although on the third day after transplantation >34% of patients receiving MPA concentration-controlled treatment had a MPA AUC_{12} <30 μg • h/mL, treating clinicians did not make dosage changes that were sufficient to achieve the target AUC_{12}.[53]

Importantly, for those clinicians that are using therapeutic drug monitoring, predose concentrations seen with enteric-coated mycophenolate sodium do not necessarily reflect overall MPA exposure.[54] In a *post hoc* pooled analysis of three trials, renal

transplant patients (n = 88) treated with enteric-coated mycophenolate sodium or mycophenolate mofetil had median predose MPA concentrations of 2.40 and 1.83 μg/mL; in 3% of samples from enteric-coated mycophenolate sodium recipients, MPA concentrations were ≥15 μg/mL.[54] Therefore, dose adjustment according to predose concentrations could lead to inadequate MPA exposure if enteric-coated mycophenolate sodium dosages are adjusted downward in response to high predose concentrations in some patients.[54]

4. Therapeutic Efficacy

A number of studies have evaluated the efficacy of enteric-coated mycophenolate sodium in preventing renal graft rejection, with the bulk of the evidence relating to its use in ciclosporin microemulsion-based regimens. This section focuses on findings from randomized, double-blind, multinational trials comparing enteric-coated mycophenolate sodium with mycophenolate mofetil[25,41] (section 4.1), and pooled analyses of large (n >450), prospective substudies of patients receiving enteric-coated mycophenolate sodium (myPROMS [myfortic Prospective Multicenter Study])[55,56] [section 4.2]. Data are also presented from extensions of the randomized trials[57-59] (section 4.1) and substudies of diabetic patients.[60] All data are fully published.

Promising results have been seen with enteric-coated mycophenolate sodium in regimens not based on ciclosporin microemulsion (enteric-coated mycophenolate sodium plus tacrolimus with corticosteroids[45] or induction with daclizumab and antithymocyte globulin[61]) in renal transplant recipients. Corticosteroid-sparing regimens have also been evaluated in renal transplant recipients receiving enteric-coated mycophenolate sodium.[62,63] Enteric-coated mycophenolate sodium also produced promising results in paediatric renal transplant patients receiving maintenance immunosuppressive therapy after patients were switched from mycophenolate mofetil.[64] However, as enteric-coated mycophenolate sodium is specifically approved for use with ciclosporin and corticosteroids, and is not currently approved for use with tacrolimus or in paediatric patients, these studies are not discussed further.

There is also interest in reducing exposure to calcineurin inhibitors in order to prevent chronic allograft nephrotoxicity, and three studies have shown the potential of enteric-coated mycophenolate sodium in calcineurin inhibitor-free, enteric-coated mycophenolate sodium plus sirolimus- or everolimus-based regimens,[65-67] with two of these also using corticosteroid-sparing approaches.[66,67] Findings from the non-calcineurin-based regimens are all preliminary and/or based on small (n <50) noncomparative studies and are not discussed further.

4.1 Comparisons with Mycophenolate Mofetil

Randomized, double-blind, double-dummy, multinational, 12-month trials in *de novo*[41] renal transplant patients and renal transplant patients receiving maintenance immunosuppressive therapy[25] evaluated the efficacy of enteric-coated mycophenolate sodium in preventing renal graft rejection (see table II for dosage and design details).

Patients enrolled were aged 18–75 years[25,41] and recipients of first,[41] or first or second[25] deceased or living donor kidney transplants. In the maintenance treatment trial,[25] patients had received transplants ≥6 months previously, had stable graft function and were receiving a ciclosporin microemulsion and mycophenolate mofetil immunosuppressive regimen, with or without corticosteroids.

In the *de novo* treatment trial,[41] patients were randomized to receive enteric-coated mycophenolate sodium 720 mg twice daily or mycophenolate mofetil 1000 mg twice daily. Treatment was initiated within 48 hours of reperfusion of the transplanted kidney and continued for 12 months. In all patients, ciclosporin microemulsion treatment was initiated within 24 hours, with dosage adjusted to achieve target blood ciclosporin trough concentrations. Corticosteroids were tapered according to local practice, although maintaining a dosage equivalent to prednisone ≥5 mg/day for at least 6 months. Antibody induction therapies were used according to local

Table II. Efficacy of enteric-coated mycophenolate sodium (EC-MPS) in *de novo*[41] renal transplant patients (pts) and in renal transplant pts receiving maintenance immunosuppressive therapy.[25] Results of modified intention-to-treat analyses from randomized, double-blind, multinational, 12-month trials comparing EC-MPS with mycophenolate mofetil (MMF)

Study	Treatment (mg bid)	No. of pts	Timepoint (mo)	Endpoint (% of pts)				
				treatment failure[a]	biopsy-proven acute rejection, graft loss or death	biopsy-proven acute rejection	biopsy-proven chronic rejection	graft loss or death
***De novo* renal transplant pts**								
Salvadori et al.[41]	EC-MPS 720	213	6	25.8[b]				
			12	28.6	26.3	22.5	2.8	5.2
	MMF 1000	210	6	26.2[b]				
			12	28.1	28.1	24.3	6.2	6.7
Maintenance treatment renal transplant pts								
Budde et al.[25][c]	EC-MPS 720	159	12	7.5	2.5	1.3	3.8	1.3
	MMF 1000	163	12	12.3	6.1	3.1	4.9	3.1

a Defined as the incidence of biopsy-proven acute graft rejection, graft loss, death or loss to follow-up.[25,41]

b Primary endpoint. Clinical equivalence was concluded as the 95% CI for the between-group difference in event rates was within the limits −12, +12.[41]

c Tolerability measures were the primary endpoint in this trial.

bid = twice daily.

protocols, as was cytomegalovirus (CMV) prophylaxis.[41] In the maintenance treatment trial,[25] patients received mycophenolate mofetil 1000 mg twice daily during a 14-day run-in period, and were then randomized to receive enteric-coated mycophenolate sodium 720 mg twice daily or mycophenolate mofetil 1000 mg twice daily for 12 months. Target blood ciclosporin trough concentrations were 100–200 ng/mL and oral corticosteroids were administered in line with local practice, but at a steady dosage during the first 3 months.

Efficacy assessments were completed at 6 and 12 months.[25,41] The composite primary endpoint in the *de novo* treatment trial was treatment failure at 6 months, which included biopsy-proven acute rejection, graft loss, death or loss to follow-up.[41] Tolerability assessments were the primary endpoints in the maintenance treatment trial (section 5).[25] Secondary endpoints included treatment failure at 12 months, biopsy-proven acute rejection, graft loss or death, biopsy-proven chronic rejection, and a composite measure of biopsy-proven acute rejection, graft loss or death.[25,41] In the *de novo* treatment trial,[41] clinical equivalence between enteric-coated mycophenolate sodium and mycophenolate mofetil was concluded if the 95% CI for the difference in event rate for the primary endpoint was within the limits −12, +12. Efficacy analyses used data from all randomized patients with at least one efficacy assessment (modified intention-to-treat [ITT] analyses).[25,41]

In the *de novo* treatment trial,[41] 213 patients were randomized to enteric-coated mycophenolate sodium and 210 to mycophenolate mofetil. There were no significant baseline differences in demographic and clinical characteristics between treatment groups. In the enteric-coated mycophenolate sodium and mycophenolate mofetil groups, the mean patient age was 47.1 and 47.2 years, 64.3% and 67.6% were male, 85.0% and 82.4% received deceased donor kidneys, 16.9% and 12.4% were donor CMV positive/recipient CMV negative, and 20.7% and 13.3% had cold ischaemia times ≥24 hours. Of the patients randomized to enteric-coated mycophenolate sodium, 151 (70.9%) completed 12 months of study treatment compared with 158 (75.2%) patients randomized to mycophenolate mofetil, with the majority who discontinued doing so because of adverse events (16.9% of enteric-coated mycophenolate sodium recipients vs 13.8% of mycophenolate mofetil recipients).

In the maintenance treatment trial,[25] 159 patients were randomized to receive enteric-coated mycophenolate sodium and 163 to receive mycophenolate mofetil. There were no significant differences between groups in terms of baseline characteristics. In the enteric-coated mycophenolate sodium and mycophenolate mofetil groups, the mean ages were 48.6 and 46.8 years, 61% and 70.6% were male, 90.6% and 87.7% were receiving a first kidney transplant, patients were recruited a mean 844 and 864 days after transplant, mean serum creatinine levels were 141.2 and 138.8 μmol/L, 84.9% and 85.3% were receiving corticosteroids, and the mean ciclosporin trough concentrations were 188.9 and 190.1 ng/mL. In the enteric-coated mycophenolate sodium group, 10.1% of patients discontinued treatment prematurely and 5.7% discontinued because of adverse events, with corresponding rates in the mycophenolate mofetil group of 11.7% and 2.5%.[25]

Enteric-coated mycophenolate sodium had similar efficacy to mycophenolate mofetil in the prevention of renal transplant rejection in *de novo*[41] renal transplant patients and renal transplant patients receiving maintenance immunosuppressive therapy.[25] For the primary endpoint in the *de novo* treatment trial,[41] the efficacy of enteric-coated mycophenolate sodium was equivalent to that of mycophenolate mofetil, with a treatment failure rate at 6 months of 25.8% versus 26.2% (between-group difference 95% CI −8.7, +8.0) [table II].

In *de novo*[41] renal transplant patients and renal transplant patients receiving maintenance immunosuppressive therapy,[25] there was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil in the proportion of patients experiencing biopsy-proven acute rejection, biopsy-proven chronic rejection, graft loss or death, or the composite of biopsy-proven acute graft rejection, graft loss or death at 12 months (table II).[41] Moreover, renal transplant patients receiving maintenance immunosuppressive therapy could be switched from mycophenolate mofetil to enteric-coated mycophenolate sodium without affecting efficacy.[25]

In the *de novo* treatment trial, severe acute rejection episodes (Banff grade III) occurred in 2.1% of enteric-coated mycophenolate sodium recipients and 9.8% of mycophenolate mofetil recipients.[41] In this trial, antibody induction therapy was administered to 39.4% of enteric-coated mycophenolate sodium recipients and 42.9% of mycophenolate mofetil recipients. In addition, there were no significant differences between patients receiving enteric-coated mycophenolate sodium and those receiving mycophenolate mofetil in the mean corticosteroid dosage at 12 months (0.1 vs 0.1 mg/kg/day), the mean ciclosporin microemulsion dosage at 12 months (3.5 vs 3.2 mg/kg/day) or the mean blood ciclosporin trough concentration at 12 months (166.3 vs 170.6 ng/mL).[41]

The efficacy of enteric-coated mycophenolate sodium in patients with diabetes was assessed in *post hoc* subgroup analyses of the *de novo* treatment trial (n = 76) and the maintenance treatment trial (n = 89).[60] In the *de novo* treatment trial, the treatment failure rate at 6 months was 14.7% in patients with diabetes receiving enteric-coated mycophenolate sodium versus 26.7% in patients receiving mycophenolate mofetil; corresponding 12-month rates were 17.6% versus 26.2% for treatment failure, 14.7% versus 19.0% for biopsy-proven acute rejection and 2.9% versus 7.1% for graft loss or death (between-group differences were nonsignificant for all comparisons). In the maintenance treatment trial, six diabetic patients died or had mild severity biopsy-proven acute rejection (three in each treatment group) and none experienced graft loss.[60]

4.1.1 Extension Studies

Patients completing these trials were enrolled in noncomparative extensions to evaluate the long-term use of enteric-coated mycophenolate sodium.[58,59] The *de novo* treatment trial extension included 247 of 367 patients (62%) who completed the core trial and who were followed-up for a further 24 months in the extension phase.[58] The maintenance treatment trial extension recruited 260 of 297 patients (88%) who completed the core trial, all of whom were included in the 12-month follow-up efficacy analyses, whereas patients who discontin-

ued during the first 12 months of the extension (n = 65) were excluded from the 24-month analyses (n = 195).[59] In the extension phase, all patients (including those initially randomized to mycophenolate mofetil) received enteric-coated mycophenolate sodium 720 mg twice daily.[58,59]

There was no decline in the efficacy of enteric-coated mycophenolate sodium in *de novo* renal transplant patients and renal transplant patients receiving maintenance immunosuppressive therapy over 24 months of follow-up.[58,59] Among *de novo* renal transplant patients initially randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil, 3% and 5% experienced biopsy-proven acute rejection, 2% and 1% experienced graft loss, 5% and 2% died or experienced graft loss, and 6% and 5% had biopsy- and clinically-confirmed chronic rejection after 24 months of therapy with enteric-coated mycophenolate sodium in the extension phase.[58] Among renal transplant patients receiving maintenance immunosuppressive therapy who received enteric-coated mycophenolate sodium in the extension phase after initial randomization to enteric-coated mycophenolate sodium or mycophenolate mofetil, the composite of biopsy-proven acute rejection, graft loss or death occurred in 2% and 2% of patients at 12 months, and 8% and 3% at 24 months; biopsy-proven acute rejection occurred in 1% and 2% at 12 months, and 4% and 2% at 24 months; biopsy-confirmed chronic rejection occurred in 4% and 2% at 12 months, and 6% and 4% at 24 months; graft loss occurred in 0% and 1% at 12 months, and 2% and 2% at 24 months; and death occurred in 1% and 0% at 12 months, and 3% and 0% at 24 months.[59]

4.2 The myPROMS Study

The myPROMS study comprises a series of open-label, multinational substudies, which use a core protocol to explore the efficacy and tolerability of enteric-coated mycophenolate sodium in *de novo* renal transplant patients[55] or renal transplant patients receiving maintenance immunosuppressive therapy[56] treated with a ciclosporin microemulsion-based regimen.

Pooled data (n = 456) from three myPROMS substudies in *de novo* treatment recipients[68-71] were used to assess the efficacy of enteric-coated mycophenolate sodium as a componenet of ciclosporin microemulsion-based regimens.[55] The patients were single organ, renal transplant recipients, aged 18–75 years; one study excluded patients with a cold ischaemia time of >24 hours and recipients of grafts from deceased donors aged <10 or >60 years.[55] The studies involved randomization to either a lower or higher ciclosporin microemulsion dosage regimen[71] or early versus delayed introduction of ciclosporin microemulsion,[68,69] using ciclosporin blood monitoring to determine dosage. As well as ciclosporin microemulsion, patients received enteric-coated mycophenolate sodium 720 mg twice daily, induction therapy with basiliximab or daclizumab, corticosteroids, and *Pneumocystis jiroveci* and CMV prophylaxis according to local practice. The primary efficacy variables in the pooled analysis were incidence of treatment failure (defined as biopsy-proven acute rejection, graft loss or death) and graft function (median calculated creatinine clearance [CL_{CR}]) at 6 and 12 months in the modified ITT population. The mean age was 47.4 years, 64.0% were male, 6.1% had received a previous renal transplant, 72.6% received their graft from a deceased donor and the mean cold ischaemia time was 14.4 hours.[55]

A pooled analysis is also available from three myPROMS substudies in renal transplant patients receiving maintenance immunosuppressive therapy (n = 588).[56] First or second renal transplant recipients were eligible if they had stable graft function and had been receiving mycophenolate mofetil and ciclosporin microemulsion with or without corticosteroids for ≥3 months.[56] Patients were aged 18–75 years, although one study included patients aged >6 years; 3.1% of the entire study population were aged 6–18 years. Patients aged >18 years were switched from mycophenolate mofetil 1000, 1500, 2000 or 3000 mg/day to enteric-coated mycophenolate sodium 720, 1080, 1440 or 2160 mg/day, respectively (conversion to higher than equimolar dosages was allowed); ciclosporin microemulsion

Table III. Efficacy of enteric-coated mycophenolate sodium (EC-MPS) in *de novo*[55] renal transplant patients (pts)[56] and renal transplant pts receiving maintenance immunosuppressive therapy. Results of pooled analyses of myPROMS substudies

Study	Treatment	No. of pts	Timepoint (mo)	Treatment failure[a] (% of pts)	Biopsy-proven acute rejection (% of pts)	Chronic rejection (% of pts)	Graft loss (% of pts)	Death (% of pts)
***De novo* renal transplant pts**								
Legendre et al.[55]	EC-MPS 720 mg bid	456	6	23.9[b]	20.6	5.3	3.1	0.9
			12	25.9[b]	22.1	6.6	3.1	1.3
Maintenance treatment renal transplant pts								
Pietruck et al.[56][c]	EC-MPS 720–2160 mg/day	588	6	1.9	1.7	0.3	0	0.2

a Defined as the incidence of biopsy-proven acute rejection, graft loss or death.[55,56]

b Primary efficacy variable.

c Tolerability measures were the primary endpoint in this study.

bid = twice daily.

and corticosteroids were also administered. Tolerability was the primary endpoint in this analysis. Secondary efficacy endpoints, assessed after 6 months of therapy, included the incidence of treatment failure (defined as biopsy-proven acute rejection, graft loss or death). Efficacy was assessed in the modified ITT population. The mean age was 43.8 years, 63.9% were male, 10.2% had received a prior renal transplant, mean time since transplantation was 37.4 months and 61.2% were recipients of grafts from deceased donors.[56]

Enteric-coated mycophenolate sodium was associated with high rates of graft survival in *de novo* renal transplant patients.[55] Approximately one-quarter of patients experienced treatment failure at months 6 and 12 (primary endpoint), with graft loss occurring in ≈3% of patients (table III).[55]

Renal transplant patients receiving maintenance immunosuppressive therapy were successfully switched from mycophenolate mofetil to enteric-coated mycophenolate sodium with low rates of treatment failure.[56] Less than 2% of patients experienced treatment failure and no patient experienced graft loss (table III).

Renal function remained stable in both *de novo*[55] renal transplant patients and in renal transplant patients receiving maintenance immunosuppressive therapy.[56] Median CL_{CR} was 58.5, 62.5 and 62.9 mL/min at months 3, 6 and 12, respectively, in *de novo* patients (primary endpoint at months 6 and 12).[55] In renal transplant patients receiving maintenance immunosuppressive therapy, mean CL_{CR} was 65.3 mL/min at baseline and 66.9 mL/min at month 6.[56]

The efficacy of enteric-coated mycophenolate sodium in patients with diabetes who underwent renal transplantation was assessed using this same pooled data from the myPROMS substudies.[60] In the analysis of *de novo* renal transplant patients, 79 of 456 (17%) had pre-transplant diabetes and there were no significant differences in 6- or 12-month efficacy variables between patients with and without diabetes at baseline. At 6 months, the treatment failure rate was 19.0% and 24.9% in diabetic and non-diabetic patients; corresponding 12-month rates were 20.3% and 27.1% for treatment failure, 17.7% and 23.1% for biopsy-proven acute rejection, and 5.1% and 4.2% for graft loss or death. Of 588 patients in the pooled analysis of renal transplant patients receiving maintenance immunosuppressive therapy, 92 (16%) had diabetes. The treatment failure and biopsy-proven acute rejection rates at 6 months were 3.3% and 2.2% in patients with diabetes at baseline versus 1.6% and 1.6% in non-diabetic patients (statistical analysis not reported). All cases of biopsy-proven acute rejection were of mild severity (Banff criteria).[60]

There is interest in reducing exposure to calcineurin inhibitors as this could lead to better renal function by reducing calcineurin-related nephrotoxicity.[69,71] *De novo* renal transplant patients were randomized to standard (n = 45) or reduced (n = 44)

ciclosporin exposure, based on different 2-hour post-dose blood ciclosporin concentration targets.[71] All patients received enteric-coated mycophenolate sodium and steroids, along with basiliximab induction. There were no differences between standard and reduced ciclosporin-exposure groups in serum creatinine (160 and 145 μmol/L at 6 months, and 163 and 162 μmol/L at 12 months) or CL_{CR} (55.3 and 61.5 mL/min at 6 months, and 56.5 and 59.7 mL/min at 12 months). There were four patients who died (one in the standard-exposure and three in the reduced ciclosporin-exposure group) and no graft losses in either treatment group.[71] In one of the myPROMS substudies in *de novo* renal transplant patients,[68,69] patients were randomized to early (day 0) [n = 97] or delayed (day 6) [n = 100] initial administration of ciclosporin microemulsion therapy, with the dosage based on ciclosporin blood monitoring. At 3 months, CL_{CR} did not differ significantly between early versus delayed ciclosporin microemulsion treatment groups (51.1 vs 53.8 mL/min) and at 12 months there were also no between-treatment differences in CL_{CR} or in rates of treatment failure, biopsy-proven acute rejection, graft loss, death or other secondary endpoints.[68] When these patients were followed-up for 30 months, there were no significant differences in median CL_{CR} (55 vs 57 mL/min for early vs delayed) and the graft survival results were favourable, with no graft losses and one patient death in the early treatment group.[69] Therefore, in these studies, there was no long-term benefit in terms of renal function from reduced-exposure ciclosporin[71] or in delaying ciclosporin treatment.[69]

5. Tolerability

Tolerability data comparing enteric-coated mycophenolate sodium 720 mg twice daily with mycophenolate mofetil 1000 mg twice daily are available from the randomized, double-blind, multinational, 12-month trials in *de novo* renal transplant patients[41] and renal transplant patients receiving maintenance immunosuppressive therapy[25] (see section 4.1 for trial details). In the maintenance treatment trial,[25] the primary endpoints were the incidence and severity of GI adverse events (see section 5.2.1) and neutropenia (neutrophil count <1500 cells/mm^3)[see section 5.1.1] at 3 months. Non-inferiority was shown if the upper limit of the 97.5% CI for the difference in incidence rate between enteric-coated mycophenolate sodium and mycophenolate mofetil was <10%.[25] Tolerability data were also obtained from the 24-month extension phases of these trials[58,59] (section 4.1).

Tolerability data are also available from the pooled analyses of the *de novo*[55] and maintenance treatment[56] myPROMS substudies (section 4.2); the primary analysis variables in the maintenance treatment analysis were the incidence of adverse events and the incidence of dose reductions or interruptions of enteric-coated mycophenolate sodium because of adverse events.[56] In addition, tolerability data have been obtained from the PROGIS (Patient Reported Outcomes in renal transplant patients with or without GI Symptoms)[72] and myTIME (Tolerability of Myfortic® in Combination with Neoral® or Tacrolimus in Renal Transplant Patients with Gastrointestinal Intolerance)[73] studies (section 5.2.2). These studies were undertaken because the tolerability measures used in the randomized trials were crude with respect to measurement of GI symptoms, and because well validated measures of patient-reported symptoms would provide better estimates of GI symptoms and burden.[72,73] Unlike the clinical trials, these studies do not provide a blinded, concurrent comparison of the tolerability of enteric-coated mycophenolate sodium with mycophenolate mofetil.

The open-label, multinational PROGIS study enrolled patients aged ≥18 years who had undergone renal transplantation ≥1 month previously and had been receiving immunosuppressive therapy, including ciclosporin, tacrolimus, sirolimus and/or mycophenolate mofetil (≈7% were receiving mycophenolate mofetil monotherapy). All patients had been treated with mycophenolate mofetil for ≥2 weeks.[72] Patients (n = 177) with mild, moderate or severe GI symptoms were converted from mycophenolate mofetil to an equimolar dosage of enteric-coated mycophenolate sodium (patients without symptoms

continued to receive mycophenolate mofetil, although results from this treatment arm are not reported). GI symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS) [higher scores indicating higher symptom burden], the Gastrointestinal Quality of Life Index (GIQLI) [assessing GI-specific Health-Related Quality of Life (HR-QOL)], and the Psychological General Well-being Index (PGWBI) [assessing HR-QOL and psychological well being]. Patients were assessed 4–6 weeks after switching to enteric-coated mycophenolate sodium. Tolerability results were reported in the per-protocol population.[72]

The open-label, multicentre, 3-month myTIME study enrolled patients aged 18–75 years (n = 734) who had undergone renal transplantation ≥1 month previously, had been receiving immunosuppressive therapy (comprising mycophenolate mofetil with ciclosporin or tacrolimus with or without corticosteroids) for ≥2 weeks, and were experiencing mild to moderate GI symptoms considered to be related to mycophenolate mofetil.[73] Patients were switched to an equimolar dosage of enteric-coated mycophenolate sodium. The primary endpoint was the change from baseline in the overall GSRS score at 3 months. Analyses were conducted in the modified ITT population (n = 728).[73]

5.1 General Adverse Event Profile

5.1.1 Comparisons with Mycophenolate Mofetil

In the maintenance treatment trial, adverse events were reported in 93.7% of enteric-coated mycophenolate sodium recipients and 92.6% of mycophenolate mofetil recipients.[25] Neutropenia (primary endpoint) occurred in 0.6% of enteric-coated mycophenolate sodium recipients and 3.1% of mycophenolate mofetil recipients, a difference in rates of 2.5% (95% CI −6.74, 0.80) during the first 3 months of the trial. A severe adverse event or infection occurred in 21.3% and 20.9% of enteric-coated mycophenolate sodium and mycophenolate mofetil recipients,[59] and 29.5% of patients in each treatment group experienced drug-related adverse events.[25]

In the *de novo* treatment trial, adverse events were reported in 98.1% of enteric-coated mycophenolate sodium recipients and 98.1% of mycophenolate mofetil recipients.[41] Most adverse events were of mild to moderate severity, with severe adverse events occurring in 38.0% of enteric-coated mycophenolate sodium recipients and 41.0% of mycophenolate mofetil recipients. There was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients in the incidence of suspected drug-related adverse events (53.1% vs 60.5%).[41] Neutropenia occurred in one enteric-coated mycophenolate sodium recipient and in one mycophenolate mofetil recipient; the absolute neutrophil count was ≥500 cells/mm^3 in all patients.[41]

Among enteric-coated mycophenolate sodium and mycophenolate mofetil recipients, CMV infection occurred in 21.6% and 20.5% of *de novo* renal transplant patients; in the corresponding treatment groups, CMV disease occurred in 4.7% and 4.3% of patients.[41] In renal transplant patients receiving maintenance immunosuppressive therapy, CMV infection was detected in 1.9% and 1.8% of enteric-coated mycophenolate sodium and mycophenolate mofetil recipients.[25]

Extension Studies

In the 24-month extensions of the *de novo*[58] and maintenance treatment[59] trials (during which all patients received enteric-coated mycophenolate sodium), adverse events occurred in 88%[58] and 92%[59] of patients originally randomized to enteric-coated mycophenolate sodium, and 89%[58] and 92%[59] of patients originally randomized to mycophenolate mofetil. Among patients originally randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil in the *de novo* treatment trial, severe adverse events occurred in 30% and 27% of patients, drug-related adverse events occurred in 27% and 30%, and discontinuations because of adverse events occurred in 11% and 13%.[58] Among patients originally randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil in the maintenance treatment trial, dose reductions or interruptions because of adverse

events occurred in 11% and 14% of patients during the 24-month extension, severe adverse events or infections occurred in 32% and 26%, and discontinuations because of adverse events occurred in 4% and 8%.[59]

Haematological events were observed with a similar incidence during extension studies, irrespective of whether patients had initially received enteric-coated mycophenolate sodium or mycophenolate mofetil during the double-blind trials.[58,59] Among *de novo* renal transplant patients originally randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil, anaemia occurred in 7% and 6% of patients, leukopenia occurred in 14% and 10%, neutropenia occurred in 3% and 0%, and thrombocytopenia occurred in 1% and 1%.[58] Among patients originally randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil in the maintenance treatment trial, anaemia occurred in 8% and 3% of patients during the 24-month extension, leukopenia occurred in 7% and 7%, neutropenia occurred in 1% and 2%, and thrombocytopenia occurred in 1% and 0%.[59]

5.1.2 The myPROMS Study

Adverse events occurred in 454 of 456 (99.6%)[55] and 370 of 588 (62.9%)[56] enteric-coated mycophenolate sodium recipients in the pooled analyses of the *de novo*[55] and maintenance treatment[56] myPROMS substudies. Approximately 60% of adverse events were of mild or moderate severity in both *de novo* renal transplant patients[55] and renal transplant patients receiving maintenance immunosuppressive therapy.[56] Adverse events or infections thought to be related to enteric-coated mycophenolate sodium occurred in 54% of *de novo* renal transplant patients and resulted in either dose adjustment or interruption of enteric-coated mycophenolate sodium in 7.5% of patients.[55] Dose reduction or interruption of enteric-coated mycophenolate sodium because of adverse events occurred in 4.1% and 1.9% of renal transplant patients receiving maintenance immunosuppressive therapy.[56]

Laboratory parameters and vital signs were stable throughout in renal transplant patients receiving maintenance immunosuppressive therapy.[56]

5.2 Gastrointestinal Adverse Events

5.2.1 Comparisons with Mycophenolate Mofetil

In the maintenance treatment trial, enteric-coated mycophenolate sodium was noninferior to mycophenolate mofetil in the overall incidence of GI adverse events (primary endpoint) at 3 months (26% vs 21%[25]) [between-group difference 95% CI −3.7, 14.8[74]]. The incidence rates for the most commonly occurring GI adverse events (e.g. nausea, diarrhoea, dyspepsia, gastro-oesophageal reflux disease, vomiting) are shown in figure 2.[25] The overall incidence of gastrointestinal adverse events at 12 months was 30% in enteric-coated mycophenolate sodium recipients and 25% in mycophenolate mofetil recipients.[25] Dose reductions and/or interruptions because of GI adverse events occurred in 8% of enteric-coated mycophenolate sodium recipients and in 6% of mycophenolate mofetil recipients, with dose discontinuation because of GI adverse events occurring in 2% of patients in each treatment group.[25]

After 12 months' follow-up in renal transplant recipients receiving maintenance immunosuppressive therapy, the mean change in the GI severity score was 0.23 in patients receiving enteric-coated mycophenolate sodium and 0.47 in patients receiving mycophenolate mofetil (between-group difference −0.24; 95% CI −0.51, 0.03).[25] GI adverse event severity scores ranged from 0 (no event) to 3 (severe event).[25]

In the *de novo* treatment trial, there was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients in the overall incidence of GI adverse events after 12 months of therapy (81% vs 80%).[41] In addition, there was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients in the proportion of patients experiencing dose reduction, dose interruption or discontinuation because of GI adverse events (15% vs 20%).[41]

Extension Studies

In the 24-month extensions of the *de novo*[58] and maintenance treatment[59] trials (during which all

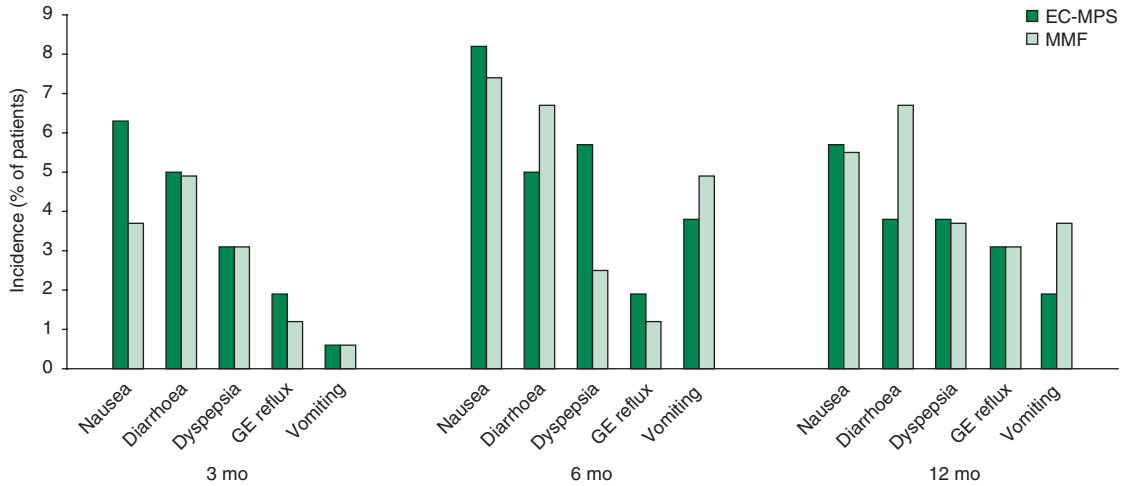

Fig. 2. Gastrointestinal (GI) tolerability of enteric-coated mycophenolate sodium (EC-MPS) 720 mg twice daily in comparison with mycophenolate mofetil (MMF) 1 g twice daily in renal transplant patients receiving maintenance immunosuppressive therapy. Incidence of most common GI adverse events after 3, 6 and 12 months of follow-up of a randomized, double-blind, multinational, 12-month trial; statistical analyses not reported.[25] **GE** = gastro-oesophageal.

patients received enteric-coated mycophenolate sodium), drug-related GI adverse events occurred in 12%[58] and 14%[59] of patients originally randomized to enteric-coated mycophenolate sodium, and 9%[58] and 8%[59] of patients originally randomized to mycophenolate mofetil. Diarrhoea was the most common drug-related GI adverse event in the maintenance treatment trial, occurring in 6% and 3% of patients originally randomized to enteric-coated mycophenolate sodium or mycophenolate mofetil.[59]

5.2.2 The PROGIS, myTIME and myPROMS Studies

Switching renal transplant patients who were experiencing GI symptoms from mycophenolate mofetil to enteric-coated mycophenolate sodium significantly reduced the burden of GI symptoms, according to the results of the PROGIS[72] and myTIME[73] studies. In the myTIME trial, the overall GSRS score (primary endpoint) was significantly reduced from baseline (i.e. during mycophenolate mofetil therapy) with enteric-coated mycophenolate sodium after 3 months of therapy (table IV), with a significant ($p < 0.0001$) difference apparent after 1 month of treatment.[73] GSRS subscale scores were significantly reduced from baseline at 4–6 weeks in the PROGIS trial,[72] and at 1 and 3 months in the myTIME trial[73] (table IV).

In the PROGIS trial, significant ($p < 0.0001$) improvements from baseline in GIQLI total and subscale scores, and PGWBI total and subscale scores were also seen after 4–6 weeks' treatment with enteric-coated mycophenolate sodium.[72]

An overall improvement from baseline in GI symptoms was reported by 66% of patients in both the PROGIS[72] and myTIME[73] trials, with 51% of patients in the PROGIS trial[72] and 55% of patients in the myTIME trial[73] reporting an improvement in HR-QOL. In the PROGIS trial, estimated minimal important differences were 0.4–0.8 for GSRS subscale scores and 0.2–0.5 for GIQLI subscale scores.[72]

GI adverse events occurred in 354 of 456 (78%)[55] and 138 of 588 (24%)[56] enteric-coated mycophenolate sodium recipients in the pooled analyses of the *de novo*[55] and maintenance treatment[56] myPROMS substudies. GI adverse events were of mild or moderate severity in 323 of 354 *de novo* renal transplant patients[55] and 137 of 138 renal transplant patients receiving maintenance immunosuppressive therapy;[56] the most commonly occurring GI adverse events included constipation,[55] nausea,[55,56] diarrhoea[55,56] and upper or lower abdominal pain.[56] Discontinuation, dose re-

duction or dose interruption of enteric-coated mycophenolate sodium because of GI adverse events occurred in 16% of *de novo* renal transplant patients in the first 12 months.[55] In renal transplant patients receiving maintenance immunosuppressive therapy, enteric-coated mycophenolate sodium dose reduction or interruption because of GI adverse events occurred in 2% and 1% of patients.[56]

5.3 Serious Adverse Events

As with other immunosuppressive agents, the US prescribing information for enteric-coated mycophenolate sodium carries a black-box warning that immunosuppression may lead to increased susceptibility to infections and to the development of lymphoma and other neoplasms.[15] It is thought that the increased risk is related to intensity and duration of immunosuppression, rather than to use of a specific agent.[14] Skin neoplasms may occur, and protective clothing and use of sunscreens to reduce exposure to sunlight is recommended.[14] It is also recommended that treating physicians are experienced in immunosuppressive therapy and organ transplantation,[14,15] with access to adequate laboratory and other medical resources.[15]

There was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients in the overall incidence of serious adverse events in either the *de novo* (55% vs 54%) renal transplant patients[41] or renal transplant patients receiving maintenance immunosuppressive therapy (23% vs 30%)[25] in 12-month trials. In the *de novo* treatment trial, there was no significant difference between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients in the incidence of serious infection (22% vs 27%), although serious pneumonia occurred in significantly fewer enteric-coated mycophenolate sodium than mycophenolate mofetil recipients (0.5% vs 4%; $p = 0.01$).[41] In the maintenance treatment trial, serious infections occurred in significantly fewer enteric-coated mycophenolate sodium than mycophenolate mofetil recipients (9% vs 16%; $p < 0.05$), although there was no significant between-group difference in the incidence of serious pneumonia (2% vs 5% of patients).[25] Other serious infections in enteric-coated mycophenolate sodium and mycophenolate mofetil recipients included urinary tract infection, pyelonephritis or urosepsis (2.5% vs 5.5%); CMV infection or CMV pneumonia (0% vs 1.2%); sepsis (1.3% vs 0%); upper respiratory tract infection (1.3% vs 0.6%); and gastroenteritis (0.6% vs 1.2%).[25]

Serious leukopenia occurred in two enteric-coated mycophenolate sodium recipients and seven mycophenolate mofetil recipients in the *de novo* treatment trial.[41]

In *de novo* renal transplant recipients, malignancies or lymphoma were reported in five enteric-coated mycophenolate sodium recipients and in five mycophenolate mofetil recipients.[41] In renal transplant patients receiving maintenance immunosuppressive therapy, lymphoma developed in two enteric-coated mycophenolate sodium recipients and one mycophenolate mofetil recipient, non-melanoma skin cancer developed in two enteric-coated mycophenolate sodium recipients and three mycophenolate mofetil recipients, and other malignancies de-

Table IV. Gastrointestinal tolerability of enteric-coated mycophenolate sodium in stable renal transplant patients (pts) with gastrointestinal symptoms switched from mycophenolate mofetil to equimolar dosages of enteric-coated mycophenolate sodium.[72,73] Mean symptom scores from the Gastrointestinal Symptom Rating Scale

Study	Assessment points	No. of pts	Abdominal pain	Reflux	Diarrhoea	Indigestion	Constipation	Overall
Chan et al.[72] (PROGIS)	Baseline	176	2.8	2.6	3.2	3.3	2.3	NA
	4–6 wk		1.9*	1.6*	2.1*	2.2*	1.7*	NA
Bolin et al.[73] (myTIME)	Baseline	728	2.5	2.3	3.0	2.8	2.2	2.6
	1 mo		1.8*	1.6*	2.0*	2.0*	1.8*	1.9*
	3 mo		1.7*	1.6*	2.0*	2.0*	1.7*	1.8*[a]

a Primary endpoint.

NA = not available. * $p < 0.0001$ vs baseline.

veloped in one enteric-coated mycophenolate sodium recipient and two mycophenolate mofetil recipients.[25,59]

In the US, there is a black-box warning that women of child-bearing potential must use contraception while taking MPA, either as enteric-coated mycophenolate sodium or mycophenolate mofetil.[15,75] It is recommended that a negative pregnancy test is obtained before initiating treatment with enteric-coated mycophenolate sodium and that effective contraception must be used before initiating treatment, during treatment and for 6 weeks after discontinuing treatment.[14,15] Enteric-coated mycophenolate sodium is not recommended for use during pregnancy and should be reserved for cases where there are no alternative treatments or where the benefits outweigh the risks to the fetus.[14,15] Mycophenolate mofetil has been associated with teratogenic effects in humans, with a number of cases reported of infants born with cleft lip and palate malformations, microtia, external auditory canal malformations, micrognathia and hypertelorism.[76] To date, there are no reports of similar malformations associated with enteric-coated mycophenolate sodium treatment. Enteric-coated mycophenolate sodium is contraindicated in breast-feeding women (in the EU),[66] or cessation of breast feeding should be taken into consideration (in the US),[15] although it is unknown whether it is excreted in breast milk.[14,15]

Enteric-coated mycophenolate sodium and mycophenolate mofetil are currently undergoing a safety review by the US FDA[15,75,77] to investigate a possible association between these drugs and the development of progressive multifocal leukoencephalopathy, a rare but life-threatening neurological disorder most commonly affecting patients with lowered immunity.

6. Dosage and Administration

Enteric-coated mycophenolate sodium is approved in the EU,[14] the US[15] and in other countries worldwide for the prevention of graft rejection following renal transplantation with allogeneic grafts. In both the EU[14] and the US,[15] it is approved for use in combination with ciclosporin and corticosteroids in adult patients.

The recommended enteric-coated mycophenolate sodium dosage is 720 mg twice daily, taken as a tablet swallowed whole and not crushed so as to preserve the enteric coating. This dosage corresponds to a dosage of mycophenolate mofetil 1000 mg twice daily, but as enteric-coated mycophenolate sodium and mycophenolate mofetil are absorbed at different rates, they should not be used interchangeably without physician supervision.[15] In patients who are newly undergoing renal transplantation, treatment with enteric-coated mycophenolate sodium should commence within 72 hours of transplantation surgery.[14] In the US,[15] it is recommended that the drug is taken on an empty stomach 1 hour before, or 2 hours after, food intake. In the EU, it is recommended that it can be taken with or without food, but that patients select one of these options and adhere to the selected option.[14]

Enteric-coated mycophenolate sodium is not approved for use in paediatric patients,[14,15] and the US prescribing information states that the safety and efficacy of enteric-coated mycophenolate sodium have not been established in paediatric *de novo* renal transplant patients.[15] However, based on the paediatric pharmacokinetic study[37] (section 3.4), the US prescribing information notes that a dosage of enteric-coated mycophenolate sodium 400 mg/m^2 BSA can be administered twice daily for stable paediatric renal transplant patients, up to a maximum of 720 mg twice daily.[15] The suggested daily dosage of enteric-coated mycophenolate sodium is 1080 mg in paediatric patients with a BSA of 1.19–1.58 m^2 and 1440 mg in patients with a BSA of >1.58 m^2.[15] The medication is given in divided doses twice daily using 180 or 360 mg tablets.[15] Doses for paediatric patients with a BSA of <1.19 m^2 cannot be accurately administered using currently available formulations of enteric-coated mycophenolate sodium.[15]

Patients with severe renal impairment (glomerular filtration rate <25 mL/min) should not be treated with enteric-coated mycophenolate sodium dosages above 1440 mg/day and should be monitored for

adverse effects that could arise from high MPA and MPAG concentrations.[14,15] Local prescribing information should be consulted for contraindications, specific warnings and precautions, specific dosage recommendations in special populations and information regarding combined use with other drugs.

7. Place of Enteric-Coated Mycophenolate Sodium in the Prevention of Renal Transplant Rejection

The European Association of Urology provides the most recent treatment guideline for renal transplantation.[1,78] The specific immunosuppression recommendations include prophylactic treatment with ciclosporin- or tacrolimus-based regimens, continued indefinitely, with protocol variations as necessary. Treatment with MPA, as mycophenolate mofetil, is recommended for use with ciclosporin and corticosteroids. In patients without acute rejection, ciclosporin and corticosteroid dosages can be reduced when mycophenolic mofetil is part of the regimen, although it is noted that there is no clinical evidence that it is safe to eliminate corticosteroids from macrolide-based induction regimens within the first 6 months of treatment. It is also recommended that patients receiving mycophenolic mofetil receive regular monitoring of bone marrow function. As the guidelines were last updated in March 2004, before enteric-coated mycophenolate sodium was available on the market, there are no specific recommendations regarding the use of enteric-coated mycophenolate sodium as a substitute for mycophenolate mofetil.[1,78]

MPA is a reversible, noncompetitive inhibitor of IMPDH, which is a first-line treatment for prophylaxis against graft rejection in kidney transplant recipients.[5,79] Mycophenolate mofetil was the first commercially available oral prodrug of MPA. It is more effective in preventing rejection episodes and is associated with better graft function than azathioprine,[80] and, increasingly, mycophenolate mofetil has replaced azathioprine in immunosuppressive treatment regimens.[5] Patients treated with ciclosporin-based regimens that include mycophenolate mofetil from the induction phase onward achieve good outcomes, with ≈90% graft survival and <20% rejection episodes by 1 year.[80] However, mycophenolate mofetil treatment is associated with adverse GI events, including gastritis, diarrhoea, anorexia, nausea and vomiting;[6,9] dose reductions or interruptions to ameliorate GI symptoms may be associated with acute graft rejection and lower graft survival in the first year following transplantation.[6,81]

Enteric-coated mycophenolate sodium was developed with the aim of achieving improved GI tolerability, in order to provide an alternative to mycophenolate mofetil.[12] Findings from pharmacokinetic studies in renal transplant patients treated with enteric-coated mycophenolate sodium are consistent with a delayed release of MPA beyond the upper GI tract (section 3.1). Although there are concerns about greater pharmacokinetic variability,[42] the available data suggest that MPA exposure and pharmacodynamic response with enteric-coated mycophenolate sodium treatment are not significantly different from those with mycophenolate mofetil (sections 2 and 3). As with mycophenolate mofetil, MPA exposure with enteric-coated mycophenolate sodium early after transplantation is reduced compared with exposure later in treatment.[14,34]

Mycophenolate mofetil dose reductions and discontinuations are associated with an increased risk of acute graft rejections[48,82] and lower graft survival,[10,11,83] suggesting that better outcomes could be obtained if MPA exposure was optimized. An intensified enteric-coated mycophenolate sodium dosage regimen early in treatment was effective in ensuring consistent, higher MPA exposure,[26] and may represent a useful advance in management, as preliminary findings on the efficacy and tolerability of an intensified dosage regimen are encouraging.[84] Further testing of this strategy is required to demonstrate that it produces better outcomes.[84]

High variability in MPA pharmacokinetics with mycophenolate sodium and mycophenolate mofetil means that treatment optimization may be difficult with fixed-dose regimens and that therapeutic drug monitoring may be useful to ensure optimal expo-

sure to MPA.[12] Unfortunately, MPA trough concentrations do not predict exposure and prospective studies are needed to assess the efficacy and feasibility of therapeutic drug monitoring.[12] Although findings from a first trial of therapeutic drug monitoring in *de novo* renal transplant recipients receiving mycophenolate mofetil were promising (section 3.5), a second trial found no benefit to therapeutic drug monitoring, although the negative findings may have arisen because the treating clinicians did not raise dosages to the extent required by the concentration-dependent dosage regimen.[53] Further randomized trials are necessary, as the positive trial was an open-label trial and the feasibility of transferring the specific AUC sampling strategy used to other clinical settings is unknown.[51] There are no trials of therapeutic drug monitoring using enteric-coated mycophenolate sodium.[51]

For clinicians using some form of therapeutic drug monitoring, it is important to note that predose MPA concentrations are higher with enteric-coated mycophenolate sodium than with mycophenolate mofetil, but that this does not indicate higher exposure.[54] This means that the enteric-coated mycophenolate sodium dosage should not be adjusted downward in response to higher predose concentrations that may be observed after switching formulations.

Children undergoing renal transplantation who are treated off label with enteric-coated mycophenolate sodium with dosages determined by BSA have a slightly higher MPA exposure than adults.[37] A more conservative strategy would be to determine dosage according to bodyweight, although dosage recommendations are available for children using surface body area for children whose BSA is ≥1.19 m^2 (section 6).[15]

In well designed trials in patients receiving standard ciclosporin emulsion-based regimens (section 4.1), enteric-coated mycophenolate sodium and mycophenolate mofetil showed equivalent efficacy in *de novo* transplant recipients,[41] while in stable renal transplant patients receiving maintenance immunosuppressive therapy, there were no significant differences between treatment groups for any efficacy endpoint.[25] Good results with maintenance treatment, including low rates of graft rejection, were achieved when treatment with enteric-coated mycophenolate sodium was continued for 12 months in the myPROMS substudies (section 4.2) and for 36 months in the extensions of the pivotal randomized trials (section 4.1.1). In *de novo* renal transplant patients treated with mycophenolate sodium in the myPROMS studies, there was no loss of efficacy in the reduced- or delayed-exposure ciclosporin microemulsion treatment groups compared with standard ciclosporin microemulsion dosage regimens (section 4.2).[68,69,71] The treatment benefits seen in these studies applied equally to the subpopulation of patients with diabetes.[60]

Enteric-coated mycophenolate sodium is currently approved for use in combination with ciclosporin and corticosteroids (section 6). Findings from studies of the use of enteric-coated mycophenolate sodium with corticosteroid-sparing regimens,[63,85] tacrolimus-based regimens,[61] and sirolimus- and everolimus-based regimens[65-67] suggest that similar positive outcomes occur with these regimens. However, further study is required before drawing firm conclusions about the efficacy of enteric-coated mycophenolate sodium in non-ciclosporin-based regimens.

Enteric-coated mycophenolate sodium had a similar tolerability profile to mycophenolate mofetil in well designed trials in *de novo* renal transplant patients and stable renal transplant patients receiving maintenance immunosuppressive therapy (section 5.1.1). As with other immunosuppressive drugs, in the US, enteric-coated mycophenolate sodium carries a black-box warning regarding an increased risk of infections and neoplasms with immunosuppressive treatment (section 5.3). However, significantly fewer enteric-coated mycophenolate sodium than mycophenolate mofetil recipients developed serious pneumonia in the *de novo* treatment trial and serious infections in the maintenance treatment trial (section 5.3). There was no difference between treatment groups in the rate of neutropenia in the first 3 months of treatment and, for enteric-coated mycophenolate sodium, ≤3% experienced neutropenia

over 36 months of treatment in extensions of the pivotal trials (section 5.1.1). Overall, a small number of patients (≤3%) developed lymphoma or non-melanoma skin carcinomas.

GI adverse events are a focus of special attention as they occur commonly in patients receiving immunosuppressive treatments and are associated with dose reductions and interruptions (with the potential for an increased risk of graft failure), non-adherence to treatment and a lower HR-QOL.[11,86] The more recent identification of the acylMPAG metabolite, which also inhibits IMPDH and which might produce a local inflammatory effect, adds further interest to this area of investigation (section 2). However, a number of factors complicate study into GI intolerance. For instance, GI symptoms are especially common in renal transplant patients. A large Scandinavian cross-sectional epidemiological survey of adult renal transplant patients reported a high prevalence of indigestion (83% of patients), abdominal pain (69%), constipation (58%) and reflux (47%).[86] The possible causes include transplant surgery itself, concurrent illnesses such as GI infections or diabetes, and individual or additive effects of immunosuppressive drugs and concomitant medications.[87] Finally, difficulty in measuring upper and lower GI tract symptoms constitutes another obstacle to a proper understanding of GI effects.[6]

In well designed trials of unselected *de novo* renal transplant patients or stable renal transplant patients receiving maintenance immunosuppressive therapy, the overall incidence of GI adverse events was similar between enteric-coated mycophenolate sodium and mycophenolate mofetil recipients (section 5.2.1). Furthermore, there was no clear difference in dose reductions, interruptions or withdrawals because of GI adverse events between the two formulations.[25,41] In the extension studies,[57-59] infections and GI events were the most common adverse events for patients receiving enteric-coated mycophenolate sodium. However, in the myTIME and PROGIS studies, patients selected for having GI symptoms associated with mycophenolate mofetil treatment consistently experienced significant reductions in GI symptoms and improved HR-QOL after switching to enteric-coated mycophenolate sodium (section 5.2.2). It should be noted that the myTIME and PROGIS studies were noncomparative studies using non-randomly selected clinical samples and that well controlled trials are needed to confirm these preliminary findings.

In the myPROMS studies, three-quarters of *de novo* renal transplant patients reported GI symptoms in the first year of treatment with enteric-coated mycophenolate sodium and nearly a fifth experienced dose reductions or interruptions or discontinued treatment (section 5.2.2). GI adverse event rates were much lower in stable renal transplant patients receiving maintenance immunosuppressive therapy, with only one patient with severe GI symptoms over a 12-month period (section 5.2.2). These studies suggest that although GI symptoms are problematic early in treatment, enteric-coated mycophenolate sodium is associated with a low rate of GI adverse events in stable renal transplant patients receiving maintenance immunosuppressive therapy.

It is difficult to reach a definitive interpretation of the GI tolerability findings. Initiating treatment with enteric-coated mycophenolate sodium does not lead to fewer GI adverse events, fewer dose reductions or discontinuations than initiating treatment with mycophenolate mofetil (section 5.2.1)[25,41,88] but patients receiving mycophenolate mofetil who develop GI symptoms appear to benefit from a switch to enteric-coated mycophenolate sodium.[72,73] However, it is well understood that in renal transplant patients, not all GI symptoms are attributable to the immunosuppressive regimen and that symptoms resolve without need for change in ≈50%.[87,89] Therefore, reducing the dosage of immunosuppressive agents should be avoidable, and adjusting the regimen should not be the first step in the management of GI symptoms with mycophenolate mofetil or with enteric-coated mycophenolate sodium. Davies et al.[87] suggest first trying other strategies, including monitoring without intervention patients who are not severely ill, further medical investigations such as stool cultures, treatment of detected conditions and empirical treatments such as dietary changes or

antidiarrhoeal agents. A similar step-wise strategy is suggested by Maes et al.,[89] commencing with stopping non-immunosuppressive drugs and proceeding with microbiological and serological investigations before changing the immunosuppressive agent.

In conclusion, enteric-coated mycophenolate sodium has a delayed absorption from the GI tract in comparison with mycophenolate mofetil, thereby potentially reducing GI adverse events. In randomized, double-blind trials of *de novo* and maintenance immunosuppressive therapy in renal transplant patients receiving ciclosporin emulsion-based regimens, enteric-coated mycophenolate sodium was as effective as mycophenolate mofetil in preventing renal graft rejection. Enteric-coated mycophenolate sodium provides an alternative to mycophenolate mofetil in the treatment of *de novo* renal transplant recipients and ongoing research should indicate whether an intensified dosage regimen can further improve clinical outcomes. Renal transplant patients receiving mycophenolate mofetil maintenance immunosuppressive therapy may be switched to enteric-coated mycophenolate sodium without compromising efficacy.

The general tolerability profile of enteric-coated mycophenolate sodium was similar to that of mycophenolate mofetil. Patients selected for GI intolerance associated with mycophenolate mofetil treatment showed reductions in GI symptoms when switched to enteric-coated mycophenolate sodium, while in unselected patients in comparative trials, there was no difference between enteric-coated mycophenolate sodium and mycophenolate mofetil in GI tolerability. Enteric-coated mycophenolate sodium provides an alternative to mycophenolate mofetil in renal transplant patients receiving mycophenolate mofetil maintenance immunosuppressive therapy who have GI symptoms that have not responded to other management strategies, because they may experience improvement if switched to enteric-coated mycophenolate sodium. Thus, in association with ciclosporin-based regimens, enteric-coated mycophenolate sodium is a valuable treatment option for immunosuppressive prophylaxis in adult renal transplant recipients.

Disclosure

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. European Association of Urology. Guidelines on renal transplantation [online]. Available from URL: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Renal%20Transplantation.pdf [Accessed 2008 Mar 10]
2. The Organ Procurement and Transplantation Network. US transplantation data: kidney [online]. Available from URL: http://www.optn.org/latestData/rptData.asp [Accessed 2008 Mar 14]
3. Carpenter CB, Milford EL, Sayegh MH, et al. Chapter 263: transplantation in the treatment of renal failure. In: Fauci AS, Braunwald E, Kasper L, et al, editors. Harrisons internal medicine [online]. Available from URL: http://www.accessmedicine.com [Accessed 2008 Mar 14]
4. Fellström B. Immune injury: is it all there is to chronic graft rejection? Nephrol Dial Transplant 1995; 10 (2): 149-51
5. Samaniego M, Becker BN, Djamali A. Drug insight: maintenance immunosuppression in kidney transplant recipients. Nat Clin Pract Nephrol 2006 Dec; 2 (12): 688-99
6. Arns W. Noninfectious gastrointestinal (GI) complications of mycophenolic acid therapy: a consequence of local GI toxicity? Transplant Proc 2007; 39 (1): 88-93
7. Cianco G, Burke GW, Miller J. Induction therapy in renal transplantation: an overview of current developments. Drugs 2007; 67 (18): 2667-80
8. Bullingham RES, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet 1998 Jun; 34 (6): 429-55
9. Bardsley-Elliot A, Noble S, Foster RH. Mycophenolate mofetil: a review of its use in the management of solid organ transplantation. Biodrugs 1999 Nov; 12 (5): 363-410
10. Behrend M, Braun F. Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. Drugs 2005; 65 (8): 1037-50
11. Bunnapradist S, Lentine K, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. Transplantation 2006 Jul 15; 82 (1): 102-7
12. Budde K, Glander P, Diekmann F, et al. Review of the immunosuppressant enteric-coated mycophenolate sodium. Expert Opin Pharmacother 2004 Jun; 5 (6): 1333-45
13. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. Drugs 2005; 65 (6): 799-805
14. European Medicines Agency. Myfortic (mycophenolate sodium): summary of product characteristics [online]. Available from URL: http://www.emc.medicines.org.uk [Accessed 2008 Mar 10]
15. Novartis. Myfortic®: prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2007/050791s001lbl.pdf [Accessed 2008 Mar 10]

16. Hummel M, Yonan N, Ross H. Pharmacokinetics and variability of mycophenolic acid from enteric-coated mycophenolate sodium compared with mycophenolate mofetil in *de novo* heart transplant recipients. Clin Transplant 2007 Jan; 21 (1): 18-23
17. Kobashigawa JA, Renlund DG, Gerosa G, et al. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in *de novo* heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. J Heart Lung Transplant 2006 Aug; 25 (8): 935-41
18. Dumortier J, Gagnieu MC, Salandre J. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in liver transplant patients presenting gastrointestinal disorders: a pilot study. Liver Transpl 2006 Sep; 12 (9): 1342-6
19. Marzano AV, Dassoni F, Caputo R. Treatment of refractory blistering autoimmune diseases with mycophenolic acid. J Dermatolog Treat 2006; 17 (6): 370-6
20. Kreuter A, Tomi NS, Weiner SM, et al. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. Br J Dermatol 2007 Jun; 156 (6): 1321-7
21. Willeke P, Schluter B, Becker H, et al. Mycophenolate sodium treatment in patients with primary Sjögren syndrome: a pilot trial. Arth Res Ther 2007; 9 (6): R115
22. McLean JE, Hamaguchi N, Belenky P, et al. Inosine 5′-monophosphate dehydrogenase binds nucleic acids *in vitro* and *in vivo*. Biochem J 2004; 379: 243-51
23. McEvoy GK, editor. AHFS drug information. Bethesda (MD): American Society of Health Pharmacists, 2007
24. Budde K, Bauer S, Hambach P, et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. Am J Transplant 2007 Apr; 7 (4): 888-98
25. 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. Am J Transplant 2003; 4 (2): 237-43
26. Budde K, Arns W, Glander P, et al. Pharmacokinetic and pharmacodynamic comparison of an initially intensified dosing regimen versus a standard dosing regimen of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant patients [abstract no. 717]. Transplantation 2008 Jul 27; 86 Suppl. 2S: 251
27. Böhler T, Canivet C, Galvani S, et al. Pharmacodynamic monitoring of the conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in stable kidney-allograft recipients. Int Immunopharmacol 2008 May; 8 (5): 769-73
28. Patel CG, Richman K, Yang D, et al. Effect of diabetes mellitus on mycophenolate sodium pharmacokinetics and inosine monophosphate dehydrogenase activity in stable kidney transplant recipients. Ther Drug Monit 2007 Dec; 29 (6): 735-42
29. Shipkova M, Armstrong VW, Wieland E, et al. Identification of glucoside and carboxyl-linked glucuronide conjugates of mycophenolic acid in plasma of transplant recipients treated with mycophenolate mofetil. Br J Pharmacol 1999; 126: 1075-82
30. Heller T, van Gelder T, Budde K, et al. Plasma concentrations of mycophenolic acid acyl glucuronide are not associated with diarrhea in renal transplant recipients. Am J Transplant 2007 Jul; 7 (7): 1822-31
31. Arns W, Breuer S, Choudhury S, et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clin Transplant 2005 Apr; 19 (2): 199-206
32. Tedesco-Silva H, Bastien MC, Choi L. Mycophenolic acid metabolite profile in renal transplant patients receiving enteric-coated mycophenolate sodium or mycophenolate mofetil. Transplant Proc 2005 Mar; 37 (2): 852-5
33. Arns W, Gies M, Choi L, et al. Absorption characteristics of EC-MPS: an enteric-coated formulation of mycophenolic sodium. Int J Clin Pharmacol Ther 2006 Aug; 44 (8): 375-85
34. Stracke S, Mayer J, Keller F, et al. Mycophenolate sodium (EC-MPS) in kidney transplant recipients under cotherapy with cyclosporine: pharmacokinetics in the early phase post transplantation [abstract no. 1253]. World Transplant Congress: The First Joint International Transplant Meeting; 2006 Jul 22-27; Boston (MA), 489
35. Arns WW, Glander P, Schuhmann R, et al. Conversion from tacrolimus to everolimus does not influence the pharmacokinetic but increases pharmacodynamic response of mycophenolate sodium in renal transplant patients [abstract no. 1248]. World Transplant Congress: The First Joint International Transplant Meeting; 2006 Jul 22-27; Boston (MA), 488
36. Budde K, Glander P, Schuhmann R, et al. Conversion from cyclosporine to everolimus leads to better renal function and to profound changes in everolimus and mycophenolate metabolism [abstract no. 2867]. World Transplant Congress: The First Joint International Transplant Meeting; 2006 Jul 22-27; Boston (MA), 999
37. Ettenger R, Bartosh S, Choi L, et al. Pharmacokinetics of enteric-coated mycophenolate sodium in stable pediatric renal transplant recipients. Pediatr Transplant 2005 Dec; 9 (6): 780-7
38. Shaw LM, Holt DW, Oellerich M, et al. Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. Ther Drug Monit 2001; 23 (4): 305-15
39. Sumethkul V, Na-Bangchang K, Kantachuvesiri S, et al. Standard dose enteric-coated mycophenolate sodium (Myfortic) delivers rapid therapeutic mycophenolic acid exposure in kidney transplant recipients. Transplant Proc 2005 Mar; 37 (2): 861-3
40. Granger DK. Enteric-coated mycophenolate sodium: results of two pivotal global multicenter trials. Transplant Proc 2001; 33: 3241-4
41. 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. Am J Transplant 2003; 4: 231-6
42. Cattaneo D, Cortinovis M, Baldelli S. Pharmacokinetics of mycophenolate sodium and comparison with the mofetil formulation in stable kidney transplant recipients. Clin J Am Soc Nephrol 2007 Nov; 2 (6): 1147-55
43. Miura M, Satoh S, Inoue K, et al. Influence of lansoprazole and rabeprazole on mycophenolic acid pharmacokinetics one year after renal transplantation. Ther Drug Monit 2008 Feb; 30 (1): 46-51
44. Cattaneo D, Merlini S, Baldelli S, et al. Mycophenolic acid formulation affects cyclosporin pharmacokinetics in stable kidney transplant recipients. Ther Drug Monit 2006 Oct; 28 (5): 643-9
45. Budde K, Glander P, Kramer BK, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant recipients receiving tacrolimus: clinical, pharmacokinetic, and pharmacodynamic outcomes. Transplantation 2007 Feb; 83 (4): 417-24
46. Kaplan B, Meier-Kriesche H-U, Minnick P, et al. Randomized calcineurin inhibitor cross over study to measure the

pharmacokinetics of co-administered enteric-coated mycophenolate sodium. Clin Transplant 2005 Aug; 19 (4): 551-8

47. Puig JM, Mir M, Marin M, et al. Correlation between mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) pharmacokinetic profile in stable renal transplant (RT) patients treated with tacrolimus (FK) without steroids [abstract no. P072]. 13th Congress of the European Society for Organ Transplantation and the 15th European Transplant Coordinators Organization; 2007 Sep 29-30; Prague
48. Kiberd BA, Lawen J, Fraser AD, et al. Early adequate mycophenolic acid exposure is associated with less rejection in kidney transplantation. Am J Transplant 2004 Apr 2; 4 (7): 1079-83
49. Arns W, Cibrik DM, Walker RG, et al. Therapeutic drug monitoring of mycophenolic acid in solid organ transplant patients treated with mycophenolate mofetil: review of the literature. Transplantation 2006; 82 (8): 1004-12
50. Oellerich M, Shipkova M, Schütz E, et al. Pharmacokinetic and metabolic investigations of mycophenolic acid in pediatric patients after renal transplantation: implications for therapeutic drug monitoring. Ther Drug Monit 2000 Feb; 22 (1): 20-6
51. Oremus M, Zeidler J, Ensom MH, et al. Utility of monitoring mycophenolic acid in solid organ transplant patients: evidence report/technology assesment no.164 (prepared by the McMaster University Evidence-based Practice Centre for the Agency for Healthcare Research and Quality, US Department of Health and Human services under contract no. 290-02-0020) [online]. Available from URL: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1b.chapter.113027 [Accessed 2008 Jul 23]
52. Le Meur Y, Büchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant 2007 Nov; 7 (11): 2496-503
53. van Gelder T, Silva HT, de Fijter JW. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation 2008; 86 (8): 1043-51
54. Budde K, Tedesco-Silva H, Pestana JM, et al. Enteric-coated mycophenolate sodium provides higher mycophenolic acid predose levels compared with mycophenolate mofetil: implications for therapeutic drug monitoring. Ther Drug Monit 2007 Jun; 29 (3): 381-4
55. Legendre C, Cohen D, Zeier M, et al. Efficacy and safety of enteric-coated mycophenolate sodium in de novo renal transplant recipients: pooled data from three 12-month multicenter, open-label, prospective studies. Transplant Proc 2007 Jun; 39 (5): 1386-91
56. Pietruck F, Abbud-Filho M, Vathsala A, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in stable maintenance renal transplant patients: pooled results from three international, multicenter studies. Transplant Proc 2007; 39 (1): 103-8
57. Salvadori M. Long-term administration of enteric-coated mycophenolate sodium in kidney transplant patients (ERL 8301 Study Group). Transplant Proc 2005 Mar; 37 (2): 909-11
58. Salvadori M, Holzer H, Civati G, et al. Long-term administration of enteric-coated mycophenolate sodium (EC-MPS; myfortic®) is safe in kidney transplant patients. Clin Nephrol 2006 Aug; 66 (2): 112-9
59. Budde K, Knoll G, Curtis J, et al. Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, myfortic®). Clin Nephrol 2006 Aug; 66 (2): 103-11
60. Pietruck F, Budde K, Salvadori M, et al. Efficacy and safety of enteric-coated mycophenolate sodium in renal transplant patients with diabetes mellitus: *post hoc* analyses from three clinical trials. Clin Transplant 2007 Jan; 21 (1): 117-25
61. Ciancio G, Burke GW, Gaynor JJ, et al. Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplant recipients given tacrolimus and daclizumab/thymoglobulin: one year follow-up. Transplantation 2008 Jul 15; 86 (1): 67-74
62. Vincenti F, Schena FP, Paraskevas S, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant 2008 Feb; 8 (2): 307-16
63. Del Castillo D, Franco A, Tabernero JM, et al. A mycophenolate sodium-based regimen with steroid withdrawal versus standard regimen in the prevention of acute rejection in kidney transplantation [abstract no. 1184]. Am J Transplant 2007 May; 7 Suppl. 2: 451
64. de Paula Meneses R, Halusch Kotsifas C. Benefits of conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in pediatric renal transplant patients with stable graft function. Pediatr Transplant. Epub 2008 Jul 30
65. Holdaas H, Bentdal O, Pfeffer P, et al. Early, abrupt conversion of *de novo* renal transplant patients from cyclosporine to everolimus: results of a pilot study. Clin Transplant 2008 May-Jun; 22 (3): 366-71
66. Rajab A, Pelletier RP, Henry ML, et al. A prospective study of steroid free, calcinurein inhibitor free maintenance immunosuppression based on Rapamune/Myfortic in kidney transplantation, an interim analysis [abstract no. 1148]. Am J Transplant 2007 May 1; 7 Suppl.2: 442
67. Kumar MSA, Khan SM, Malat GE, et al. Outcome of calcineurin inhibitor (CNI) withdrawal and conversion to triple therapy with chronic basiliximab infusion, sirolimus (SRL) and enteric coated mycophenolic sodium (EC-MPS) in kidney recipients with biopsy proven moderate/severe chronic allograft nephropathy and graft dysfunction [abstract no. 1475]. Am J Transplant 2007 May 1; 7 Suppl. 2: 527
68. Kamar N, Garrigue V, Karras A. Impact of early or delayed cyclosporine on delayed graft function in renal transplant recipients: a randomized, multicenter study. Am J Transplant 2006 May; 6 (5 Pt 1): 1042-8
69. Mourad G, Karras A, Kamar N, et al. Renal function with delayed or immediate cyclosporine microemulsion in combination with enteric-coated mycophenolate sodium and steroids: results of follow up to 30 months post-transplant. Clin Transplant 2007 May-Jun; 21 (3): 295-300
70. Cibrik D, Meier-Kriesche H-U, Bresnahan B, et al. Renal function with cyclosporine C2 monitoring, enteric-coated mycophenolate sodium and basiliximab: a 12-month randomized trial in renal transplant recipients. Clin Transplant 2007 Mar; 21 (2): 192-201
71. Budde K, Bosmans JL, Sennesael J. Reduced-exposure cyclosporine is safe and efficacious in de novo renal transplant recipients treated with enteric-coated mycophenolic acid and basiliximab. Clin Nephrol 2007 Mar; 67 (3): 164-75
72. Chan L, Mulgaonkar S, Walker R, et al. Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. Transplantation 2006 May 15; 81 (9): 1290-7

73. Bolin P, Tanriover B, Zibari GB, et al. Improvement in 3-month patient-reported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. Transplantation 2007 Dec; 84 (11): 1443-51
74. Budde K, Salvadori M. Enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF), it is better to have the choice [letter]. Am J Transplant 2005; 5 (5): 1165-6
75. US Federal Food and Drug Administration. Mycophenolate mofetil: prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2008/050722s018lbl.pdf [Accessed 2008 Sep 24]
76. Pisoni CN, D'Cruz DP. The safety of mycophenolate mofetil in pregnancy. Expert Opin Drug Saf 2008; 7 (3): 219-22
77. US Federal Food and Drug Administration. Communication about an ongoing safety review of CellCept (mycophenolate mofetil) and Myfortic (mycophenolic acid) [online]. Available from URL: http://www.fda.gov/cder/drug/early_comm/mycophenolate.htm [Accessed 2008 Apr 16]
78. Kälble T, Lucan M, Nicita G, et al. Eau guidelines on renal transplantation. Eur Urol 2005 Feb; 47 (2): 156-66
79. Kaplan B. Enteric-coated mycophenolate sodium (myfortic®): an overview of current and future use in transplantation. Drugs 2006; 66 Suppl. 2: 1-8
80. Halloran P, Mathew T, Tomlanovich S, et al. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection (the International Mycophenolate Mofetil Renal Transplant Study Groups). Transplantation 1997; 63 (1): 39-47
81. Pelletier RP, Akin B, Henry ML, et al. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. Clin Transplant 2003; 17: 200-5
82. Knoll GA, MacDonald I, Khan A, et al. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. J Am Soc Nephrol 2003 Sep; 14 (9): 2381-6
83. Hardinger KL, Brennan DC, Lowell J, et al. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. Transp Int 2004 Nov; 17 (10): 609-16
84. Arns W, Glander P, Sommerer C, et al. Comparison of an initially intensified dosing regimen versus a standard dosing regimen of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant patients: efficacy and safety analysis of 75 patients [abstract no. 266]. Transplantation 2008 Jul 27; 86 Suppl. 2S: 94
85. Schena FP, Vincenti F, Paraskevas S, et al. 12-Month results of a prospective, randomized trial of steroid avoidance, steroid withdrawal and standard steroids in *de novo* renal transplant patients receiving cyclosporine, enteric-coated mycophenolate sodium (EC-MPS, myfortic®) and basiliximab [abstract no. 54]. World Transplant Congress: The First Joint International Transplant Meeting; 2006 Jul 22-27; Boston (MA), 84-5
86. Ekberg H, Kyllönen L, Madsen S, et al. Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant recipients. Transplantation 2007 Feb 15; 83 (3): 282-9
87. Davies NM, Grinyó J, Heading R, et al. Gastrointestinal side effects of mycophenolic acid in renal transplant patients: a reappraisal. Nephrol Dial Transplant 2007 Sep; 22 (9): 2440-8
88. Kamar N, Oufroukhi L, Faure P, et al. Questionnaire-based evaluation of gastrointestinal disorders in *de novo* renal-transplant patients receiving either mycophenolate mofetil or enteric-coated mycophenolate sodium. Nephrol Dial Transplant 2005 Oct; 20 (10): 2231-6
89. Maes B, Hadaya K, de Moor B, et al. Severe diarrhea in renal transplant patients: results of the DIDACT study. Am J Transplant 2006 Jun; 6 (6): 1466-72

Correspondence: *Mark Sanford,* Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz

