**National PBM Drug Monograph**

# Mycophenolate Sodium (Myfortic®)

**March 2007**

**VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel**

## Executive Summary:

Mycophenolate sodium (MPS) is approved for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

### Pharmacokinetics:

- A single dose study in renal transplant recipients demonstrated that MPS meets the bioequivalence criteria for AUC (90% confidence interval [CI] within 80 – 125%) to MPS.
- Many single-and multi-dose studies report AUC and $C_{max}$ results are similar between MPS and MMF.
- Due to the presence of the enteric-coating $T_{max}$ for MPS is consistently longer than MMF's as would be expected.

### Dosing:

The dosage of MPS tablets was designed such that a 720mg dose of MPS would provide the nearest molar equivalent of MPA provided by 1000mg of MMF. The MMF daily dose of 1000mg BID is accepted based on the results of pivotal trials that have shown this to be the accepted dose for prophylaxis in renal transplantation. Daily doses of MPS 720mg and MMF 1000mg are utilized for liver transplant recipients while higher doses of MPS 2160mg and MMF 3000mg are used for heart transplant recipients.

- Data from trials converting from MMF to MPS in renal transplant recipients at various time intervals fail to demonstrate any statistically significant difference in interruption, reduction, discontinuation or the combination. Trials in *de novo* transplant recipients over time periods up to 36 months also fail to show any significant difference between MMF and MPS.
- Published data has demontrated the impact of GI adverse events (AEs) on health related quality of life (HRQOL). Recent data in renal transplant recipients using scores from validated questionnaires indicates that patients who have experienced GI side effects from MMF or intolerance leading to discontinuation of MMF may tolerate MPS with an improvement in total and subscale scores.

### Safety:

### Efficacy:

- The ERL B301 study group conducted a phase III, double-blind, randomized, multicenter, parallel to evaluate the therapeutic equivalence (efficacy failure) of MPS with MMF in 423 *de novo* renal transplant patients. The incidence of efficacy failure at 6 months was 25.8% and 26.2% for MPS and MMF, respectively (95% CI of -8.7, +8.0) with similar results at 12 months. The authors concluded that MPS and MMF were therapeutically equivalent.
- The ERL B302 study group conducted a phase III, randomized, double-blind, multicenter, parallel comparison of 163 patients maintained on MMF with 159 patients converted to an equimolar doseof MPS.[3] The authors described no statistical difference in BPAR, BPCRR or combined efficacy (BPAR, BPCR, death or graft loss).In the open-label phase of this trial all patients were given MPS with data of 12 and 24 months duration now available. The authors continued to conclude that patients may be safely converted to an equimolar dose of MPS.
- The *my*PROMS program is a prospective, open-label, multicenter, international study. Two subprotocols, DE02 (Europe), n=57, and LA01 (Latin America), n=237, describe the conversion of MMF to MPS in

maintenance renal transplant patients. In each the authors conclude that patients could be converted from MMF to MPS without adversely affecting safety or efficacy.

- Efficacy located for liver transplant recipients is limited to one retrospective and four prospective single-arm trials with up to 100 patients each encompassing *de novo* transplant recipients, maintenance patients or both. All authors conclude that MPS is effective and safe as a primary immunosuppressant or a replacement to MMF.
- Efficacy located for heart transplant patients is limited to one randomized trial in 154 primary heart recipients that demonstrated non-inferiority of MPS to MMF.

## Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating Mycophenolate Sodium (Myfortic®, MPS, E-MPS, EC-MPS, ERL080) for possible addition to the VA National Formulary as an alternative to mycophenolate mofetil (CellCept®, MMF, RS61443); (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

## Pharmacology

Mycophenolate sodium (MPS) is an enteric coated, delayed release monosodium salt of Mycophenolate Acid (MPA).[9] The active ingredient, MPA, was first discovered in 1896 as a fermentation product of several Penicillium species.[13] While it was initially studied as an antibiotic, it was in the early 1970's that MPA was demonstrated to suppress antibody responses and prolong skin-graft survival in mice.[2] Inhibitors of inosine monophosphate dehydrogenase (IMPDH) are effective immunosuppressants[14] and MPA is a potent, selective, uncompetitive and reversible inhibitor.[1]

*In vitro* studies have demonstrated that only free MPA is available to inhibit IMPDH[17] after NADH (nicotinamide adenine dinucleotide) is released but before XMP which is the committed step in *de novo* guanosine nucleotide synthesis.[13] The structure of IMPDH also indicates that MPA inhibits the enzyme by simultaneously mimicking the nicotinamide portion of the NAD cofactor and a catalytic water molecule.[13] Clinical studies have shown MPA to be 4.8 times more active against type II IMPDH than type I, thereby increasing its selectivity toward activated lymphocytes.[18]

Enteric-coated MPS was developed for the potential to reduce MPA-associated side effects such as nausea/ vomiting, dyspepsia, abdominal pain and discomfort based on the hypothesis of sharing a similar mechanism of GI toxicity with that of non-steroidal anti-inflammatory agents (NSAIDs). Preliminary studies showed that MPA is a potent uncoupler of mitochondrial oxidative phosphorylation similar to NSAIDs. Based on this hypothesis enteric-coated MPS was developed with the potential to reduce MPA-associated side effects such as nausea and vomiting, dyspepsia, abdominal pain and stomach discomfort.[24] The MPS dosage of 720mg was designed to provide an equimolar amount of MPA to that of a 1000mg dose of MMF.

## FDA Approved Indication(s) and Off-label Uses

| A=Approved<br>O=Off-label | Atopic Dermatitis | Graft-versus-host-disease (GVHD) | Heart transplant rejection prophylaxis | Kidney Transplant rejection | Kidney Transplant rejection prophylaxis | Liver Transplant rejection prophylaxis | Lupus Nephritis | Myasthenia gravis | Pemphigus | Rheumatoid Arthritis |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mycophenolate Sodium (Myfortic®)** | O | O | O | O | A | O | O | O | O | O |
| **Mycophenolate Mofetil (CellCept)** | O | O | A | O | A | A | O | O | O | O |

Myfortic® (MPS) received FDA approval on February 27, 2004. CellCept (MMF) was first approved in capsule form in 1995 with a tablet approved in 1997 and injectable and suppository forms in 1998.

## Current VA National Formulary Alternatives

Mycophenolate mofetil is currently listed on the VA formulary as "restricted to renal transplant patients".

## Pharmacokinetics

In vitro studies demonstrated that the enteric-coated mycophenolic acid tablet does not release mycophenolic acid under acidic conditions (pH less than 5) as in the stomach but is highly soluble in neutral pH conditions as in the intestine. Following mycophenolic acid oral administration without food in several pharmacokinetic studies conducted in renal transplant patients, consistent with its enteric-coated formulation, the median delay ($t_{lag}$)in the rise of mycophenolic acid concentration ranged between 0.25 and 1.25 hours and the median time to maximum concentration ($T_{max}$) of mycophenolic acid ranged between 1.5 and 2.75 hours. In comparison, following the administration of mycophenolate mofetil, the median $T_{max}$ ranged between 0.5 and 1 hours. In stable renal transplant patients on modified cyclosporine-based immunosuppression, GI absorption, and absolute bioavailability of mycophenolic acid following the administration of mycophenolic acid delayed-release tablet was 93% and 72%, respectively. Mycophenolic acid pharmacokinetics are dose proportional over the dose range of 360 to 2,160 mg.

In the early posttransplant period, mean mycophenolic acid AUC and $C_{max}$ were approximately one-half of those measured 6 months posttransplant. The trials in other solid organ transplant types; heart and liver, have demonstrated equivalent pharmacokinetic parameters relative to MMF. There is significant intra and inter-patient variability in pharmacokinetic parameters which is dependent on organ type, concurrent immunosupresive therapy and weeks post-tranplant.

In April of 2005 single dose pharmacokinetic data was reported.[7] This phase I randomized, three-way crossover trial was conducted in 24 stable renal transplant patients to determine bioequivalence of MPS to MMF as a reference standard. Patients were at least 3 months post surgery for their first or second renal transplant and were on cyclosporine. Fourteen were on oral steroids. The sequence consisted of a 6-8 week screening period, a 48 hour treatment period followed by 7-12 days before the next treatment period began. After the final treatment period an end-of-study evaluation occurred approximately one week later. During a treatment period one of the following single doses was administered: 640mg MPS, 720mg MPS or 1000mg MMF. The sample size was determined based on unpublished results of Novartis Pharma data which anticipated an intrapatient coefficient of variation (CV) of 15% for dose-normalized $AUC_{0-t}$ and 39% for dose-normalized $C_{max}$ to achieve a 90% CI. Samples taken at 15 different time points during the 48 hour period resulted in the following data:

The authors noted that both MPS (aka EC-MPS) doses met the bioequivalence criteria for $AUC_{0-\infty}$ to the reference formulation MMF by having 90% CI within the 80-125% limit. Neither of the MPS doses met the bioequivalence criteria for $C_{max}$. This was attributed to a higher than anticipated coefficient of variation (CV > 40%). While the confidence intervals for MPAG $C_{max}$ and AUC fall within the desired limit, MPAG is not a pharmacologically active metabolite.

### Distribution, Protein Binding and Free MPA:

The mean ($\pm$ SD) volume of distribution at steady state and elimination phase for MPA is 54 ($\pm$ 25) L and 112 ($\pm$ 48) L., respectively.[12] Once absorbed MPA is highly protein bound to albumin at about 97%[25] Studies conducted with MMF have shown that impaired renal function, including both acute short-term dysfunction and chronic renal failure, cause a significant reduction in the percentage of MPA bound.[29] A review by Bullingham[25] noted that the plasma MPA free fraction is constant across the clinical range of total plasma concentrations of MPA thus the total plasma concentration of MPA can be used as a surrogate of free MPA concentrations. Analysis of free concentrations of MPA 2 and 12 hours after MPS administration found a free fraction of MPA of approximately 1.5%. [30]

### Metabolization:

Once released, MPA has a mean half-life of 11.7 hours with a mean clearance of 8.6L/h.[31] It in turn is subject to three different metabolic pathways.[32] Two metabolites are formed via glucuronidation; mycophenolate acid glucuronide (MPAG)[31] are the most widely recognized pathways with the other being M-2, Acyl glucuronide, AcMPAG. MPAG is considered pharmacologically inactive but GI bacteria gluronidases converted it back to MPA which undergoes hepatic recirculation[20] providing a second MPA peak at ~8 hours post dose.[9] The mean half-life of

MPAG is approximately 15.7 hours with a mean clearance of 0.45L/hour[9] and is highly protein bound at 82%[20]. Tedesco-Silva et al studied 40 stable renal transplant patients and determined that MPS and MMF were bioequivalent with respect to AcMPAG. This level of AcMPAG exposure was deemed sufficient to potentially contribute to MPA-based immunosuppression and toxicity. Metabolism by the CYp450 system accounts for the final metabolite, M-3.

### Elimination:

The majority of MPA dose administered is eliminated in the urine primarily as MPAG (>60%) and approximately 3% as unchanged MPA following MPS administration to stable renal transplant patients. The elimination half-life of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.[12]

### $T_{max}$, $C_{max}$ and AUC:

Many of the studies reporting pharmacokinetic data are comprised of a small number of patients and / or are published in abstract form only. These studies demonstrate that with multiple doses the Cmax and AUC of MPS are greater than those seen with MMF. The studies can be separated into 2 broad groups: those performed on patients immediately post transplant and those on stable renal transplant patients or greater than 90 days post transplant.

**Effects of food:**

The effect of a high fat meal compared to the fasting state has been assessed. There was no effect on MPA AUC, along with along with a 33% decrease in $C_{max}$ and a significant delay in $T_{max}$.[9]

### Concomitant Immunosuppressive Therapy

Lower MPA concentrations between MMF-treated patients with CsA compared to those without have been described in published literature.[47,48,49,50] A similar risk may be found when using sirolimus. In their review of MPS Behrend and Braun[20] cite a publication by Kreis (2000) that compared sirolimus with CsA in combination with corticosteroids and MMF 2g/day and found higher MPA concentrations.

### Therapeutic drug monitoring:

Therapeutic drug monitoring in the context of MMF and MPS has been defined as a diagnostic method that assigns drug concentration values, based on studies relating patient outcome measurements to drug concentrations, to predict efficacy (usually a lowered rate of graft rejection) or toxicity (short-term or long-term) in individual patients.[27] Significant predictive value for acute rejection[26,51], renal function and drug-related side effects has been found for the 12h dose interval MPA $AUC_{0-12}$ and the predose trough MPA concentration ($C_0$).[52] Maximum plasma concentration ($C_{max}$) (>30mg/L) and AUC values ($\geq$ microgram*h/ml) for MPA are associated with a lower risk of renal allograft rejection; while levels of therapeutic exposure >60-70 microgram*h/ml are associated with a significant proportion of patients withdrawing from treatment due to adverse events, mainly GI intolerability.[9]

## Dosage and Administration

MPS is available in 180mg and 360mg enteric coated tablets.[12] Because of this coating the tablets should not be crushed. [12,20] The pharmacokinetic behavior of MPA and MPAG previously described in this document require that both MPS and MMF be administered twice daily. The dosage of MPS tablets was designed such that a 720mg dose of MPS would provide the nearest molar equivalent of MPA provided by 1000mg of MMF. The MMF daily dose of 1000mg BID is accepted based on the results of pivotal trials that have shown this to be the accepted dose for prophylaxis in renal transplantation.[7] Daily doses of MPS 720mg and MMF 1000mg are utilized for liver transplant recipients while higher doses of MPS 2160mg and MMF 3000mg are used for heart transplant recipients.

### Renal Impairment:

No dosage adjustments are considered necessary in patients experiencing delayed graft function postoperatively, or the elderly though patients with severe chronic renal insufficiency, defined as glomerular filtration rate of <10ml/min, should be monitored to signs and symptoms of MPA toxicities.[2,15] In contrast, MPAG exposure would be increased markedly with decreased renal function; MPAG exposure being approximately 8-fold higher in the setting of anuria. Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the high plasma protein binding of MPA.[12]

Data from a single-dose study of MMF in patients with varying degree of renal function found that MPA and MPAG clearance was not affected by a decreased glomerular filtration rate and hemodialysis did not affect MPA clearance.[18]

**Hepatic Impairment:**

No dosage adjustment is considered necessary in patients with hepatic parenchyma disease.[15]

In a single dose study of MMF in 18 patients with alcoholic cirrhosis $C_{max}$ and AUC of MPA and MPAG were lower in patients with mild impairment versus healthy volunteers, were higher in moderately impaired patients than in those mildly impaired. Patients with severe impairment had double the mean renal clearance of MPAG suggesting increased renal glucuronidation of MPA.[18]

**Dosages Reductions:**

In many cases a reduction in the daily dose is required due to side effects or enabled due to the progress of the patient on their current drug regimen.

**Dosage Conversion:**

ERL B302 Study Group

The series of 4 abstracts and 3 publications originating from this group describe a phase III, randomized, double-blind, double-dummy, multi-center, parallel comparison of 163 patients maintained on MMF 1000mg BID with 159 patients converted to 720mg BID of MPS. Patients included were 18-75 years old and at least 6 months post primary or second cadaveric or living donor kidney transplant. Exclusion criteria are noted in table below.

| | |
|---|---|
| • 3 or more kidney grafts<br>• transplant of another organ,<br>• thrombocytopenia <75K/mm$^3$,<br>• ANC of <1500cells/mm$^3$,<br>• leukocytopenia <2500cells/mm$^3$,<br>• clinically significant infection requiring continued therapy, | • presence of severe diarrhea,<br>• active peptic ulcer disease,<br>• uncontrolled DM,<br>• positive HIV,<br>• malignancy within the last 5 years,<br>• use of any investigational drug within 2 weeks before screening. |

The primary endpoint safety endpoint was the evaluation of the incidence and severity of GI AEs at 3 months and neutropenia (defined as a low absolute neutrophil count <1500 cells/mm$^3$) within the first 3 months of study administration. [3] Statistical analyses were performed on an intent to treat basis (ITT). Outcome data for this series is summarized in Table 1 at the end this section with adverse events summarized in Table 2.

There was no statistical difference in BPAR, BPCR or combined efficacy (BPAR, BPCR, death and graft loss). A comparison of all AEs, GI AEs, upper GI AEs, dyspepsia, nausea, GERD, vomiting, non-upper GI AEs, diarrhea at 3, 6 and 12 months found no statistical difference between MPS and MMF groups. Comparison of overall infection rates, as well as, subgroups of pneumonia, UTI/ pyelonephritis/ urosepsis, CMV/pneumonia CMV, sepsis, URI and gastroenteritis found no statistically significant differences with the sole exception of serious infection as noted in the abstracts. Data on drug discontinuation was also provided. In the MMF group 11.7% stopped, 2.5% due to an AE, 1.8% due to a GI AE and 1.2% due to diarrhea. In the MPS group the results were 10.1%, 5.7%, 1.9% and 0.6%, respectively. Composite data on dosage interruption, dosage adjustment and discontinuation was included. In the MMF group this occurred in 6.1% of patients due to a GI AE, 5.5% due to an upper GI AE and 4.3% due to diarrhea. In the MPS group the results were 8.2%, 4.4% and 5%, respectively. Data on the final dosage being taken was not provided. The authors concluded that patients may be safely and efficaciously converted from MMF to MPS.

At the completion of this trial an open-label extension investigating the long-term safety and tolerability of MPS as well as the safety of conversion from" MMF to MPS.[61] Patients in the MPS group continued their therapy (N = 130) while patients from the MMF study group converted to MPS 720mg BID (N = 130). Data from the first 12 months of the open-label phase found 2% of the group originally on MPS (old) decreased their medication due to an AE compared to 5% of the group converted from MMF to MPS (new) while 2% of the old group discontinued their medication compared to 6% of the new group. A comparison of BPAR, BPCR, and graft loss individually or combined found no statistical difference.

Data from 24 months of open-label usage has also been published[59,62]. After completing the core study period, 260 of 297 (88%) patients entered the open label extension phase, 130 newly exposed to MPS (converted from MMF in the open label) and 130 continuing MPS. The 260 (75%) patients completing the first 12 months were included in the 24 month extension phase (MPS newly exposed =97, MPS long term=98). The authors noted the incidence of adverse events had increased, as expected, over time and in general the overall safety profile of MPS was similar in the newly exposed and long-term groups. They also note that no new safety events occurred in patients who had been exposed for a total of 36 months.

By combining all of the adverse event data into table 2 the reader can see the incidence at different time points and up to 36 months. Of concern is the variation amongst the publications of the reported incidence of Any GI AE and CMV/Pneumonia CMV for the 0-12 month period. In each article the difference incidence for each group fails to reach statistical significance.

Table1: ERL B302 Study Group publication

| Reference | Study Type | Total (N) | Endpoints | MMF dose (mg /day) | MMF duration | Other meds | MMF (N) | MMF: # discontinued | MMF: composite interruption, adjustment or dc | MPS (N) | MPS dose finish | MPS: # decreased | MPS: # discontinued | MPS; composite (interruption, adjustment or discontinuation) | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neumayer[56] | 12mo results | 322 | Incidents and severity of gastrointestinal adverse events at 3months and neutropenia with 3 months | 2000 | | ME-CsA w/ or w/o steroids | 163 | | | 159 | | | | | Eff: EC 7.5% v MMF 12.3%, p=ns (included loss to follow-up) |
| Budde[57] | 12mo results | 322 | | 2000 | | ME-CsA w/ or w/o steroids | 163 | | | 159 | | | | | Eff: 6.1 v 2.5% p=ns |
| Budde[58] | 12mo results | 322 | | 2000 | | ME-CsA w/ or w/o steroids | 163 | | | 159 | | | | | Eff: 6.1 v 2.5% p=ns |
| Budde[3] | 12mo results | 322 | Primary safety: incidence and severity of GI AE and neutropenia within first 3 months, Secondary at 12mo; Efficacy failure, composite of BPAR, graft loss or death at 6 and 12 mo, BPCR at 6 and 12 mo | 2000 | >4wks | ME-CsA w/ or w/o steroids | 163 | 11.7%, 2.5% due to AE, 1.8% due to GI AE, 1.2% due to Diarrhea | GI AE: 6.1%, Upper GI AE: 5.5%, Diarrhea 4.3% | 159 | | | 10.1%, 5.7% due to AE, 1.9% due to GI AE, 0.6% due to diarrhea | GI AE: 8.2%, upper GI AE 4.4, diarrhea 5% | Eff: 6.1 v 2.5% p=ns, BPAR 3.1 v 1.3 p=ns, BPCR 4.9 v 3.8 p=ns |
| Budde[60] | 12mo results | 322 | Primary safety endpoints were incidence and severity of GI AE at 3mo and incidence of neutropenia within the first 3 months | 2000 | >4wks | ME-CsA w/ or w/o steroids | 163 | | | 159 | | | | | Eff: 3mo: EC 3.1% v MMF 3.7%, 6mo: 3.8% v 6.1%, 12mo: EC 7.5% v MMF 12.3%, p=ns (included loss to follow-up) |
| Budde[61] | Open-Label phase 12-24mo | 130 | Long-term safety and efficacy of MPS in *de novo* | | | | | | | 130 | Newly exposed 1420 ± 120mg/day (>97% of planned dose) | 5% due to AE | 6% | 8% | Eff: no signif diff; Composite: 2.3%; BPAR 2.3%, graft loss 0; BPCR 2% |
| | | 130 | Long-term safety and efficacy of conversion from MMF to MPS | | | | | | | 130 | Long-term pts: 1410±130mg/day (>97% of planned dose) | 2% due to AE | 2% | 11% | Eff: no signif diff; Composite: 1.5%; BPAR 0.8%, graft loss 1%; BPCR 4% |
| Budde[59] | Open-Label phase 12-36mo | 98 | Long-term safety and efficacy of MPS in *de novo* | | | | | | | 98 | | | | | Eff (BPAR,death, graft loss): 8 (8.2%); BPAR: 4 (4.1%); BPCR: 6 (6.1%); Graft loss: 2 (2.0%) |
| | | 97 | Long-term safety and efficacy of conversion from MMF to MPS | | | | | | | 97 | | | | | Eff (BPAR,death, graft loss): 3 (3.1%); BPAR: 2 (2.1%); BPCR: 4 (4.1%); Graft loss: 2 (2.1%) |
| Budde[62] | Open Label phase 12-24mo | 130 | Long-term safety and efficacy of MPS in *de novo* | | | | | | | 130 | 1410 ± 130 | 14 (12%) due to AE | 3 (2%): 1 ea GI, polyarthritis | | Eff (BPAR, death, graft loss): 2(2%), BPAR: 1(1%), BPCR 5(4%), Graft loss 0, death 1(1%) |
| | | 130 | Long-term safety and efficacy of conversion from MMF to MPS | | | | | | | 130 | 1410 ± 120 | 11 (8%) due to AE | 8(6%): GI (3), 1 each hepatic mass, malignancy, rash, | | Eff (BPAR, death, graft loss): 3(2%), BPAR: 2(2%), BPCR 3(2%), Graft loss 1(1%), death 0 |
| | Open Label phase 24-36mo | 98 | Long-term safety and efficacy of MPS in *de novo* | | | | | | | 98 | 1400 ± 140 | 11 (11%) due to AE | 9(9%): GI (3), Neutropenia (1), Polyarthritis (1) | | Eff (BPAR, death, graft loss): 8(8%), BPAR: 4(4%), BPCR 6(6%), Graft loss 2(2%), death 3(3%) |
| | | 97 | Long-term safety and efficacy of conversion from MMF to MPS | | | | | | | 97 | 1400 ± 130 | 14 (14%) due to AE | 12(12%): GI (3), Malignancy (3), hepatic mass (1), rash (1) | | Eff (BPAR, death, graft loss): 3(3%), BPAR: 2(2%), BPCR 4(4%), Graft loss 2(2%), death 0 |

Eff = efficacy

Table 2: ERL B302 Study Group publications: adverse events

| | at 3mo | | | at 6mo | | at 12mo | | 0-3 mo | | 0-12 mo | | | 12-24mo | | 24-36mo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **EC-MPS** | **MMF** | ***P* value** | **EC-MPS** | **MMF** | **EC-MPS** | **MMF** | **EC-MPS** | **MMF** | **MMF** | **EC-MPS** | ***P* value** | **New EC-MPS** | **Long-term EC-MPS** | **New EC-MPS** | **Long-Term EC-MPS** |
| Any AE | | | | | | | | | | 92.6%[abcdfh] | 93.7%[abcdfh] | ns[abd] | 86.9%[fh] | 88.5%[fh] | 92%[h] | 92%[h] |
| Severe AEs | | | | | | | | | | | | | | | 29.9%[g] | 29.6%[g] |
| Severe AE or Infection | | | | | | | | | | 21%[h] | 21%[h] | | 20%[h] | 19%[h] | 19%[h] | 32%[h] |
| Serious AEs | | | | | | | | | | 30.1[abcd] | 23.3[abcd] | ns[abcd] | | | | |
| Any GI | 26.4%[de] | 20.9%[de] | ns[d] | 28.9%[de] | 27.6%[de] | 29.6%[d] | 24.5%[d] | | | 61.0%[abc], 61.3%[d], 57.1%[f] | 60.0[abc] 60.4%[d], 56.6%[f] | ns[abd] | 44.6%[f] | 49.2%[f] | | |
| Serious GI AEs | | | | | | | | | | 4.9%[f] | 3.8%[f] | | 6.2%[f] | 4.6%[f] | | |
| Upper GI | 13.2%[de] | 13.5%[de] | | 15.7%[de] | 16.6%[de] | 15.1%[d] | 14.1%[d] | | | | | | | | | |
| Dyspepsia | 3.1%[d] | 3.1%[d] | | 5.7%[d] | 2.5%[d] | 3.8%[d] | 3.7%[d] | | | 14.7%[f] | 13.8%[f] | | 6.9%[f] | 49.2%[f] | | |
| Nausea | 6.3%[d] | 3.7%[d] | | 8.2%[d] | 7.4%[d] | 5.7%[d] | 5.5%[d] | | | 19.0%[f] | 24.5%[f] | | 6.9%[f] | 8.5%[f] | | |
| Vomiting | 0.6%[d] | 0.6%[d] | | 3.8%[d] | 4.9%[d] | 1.9%[d] | 3.7%[d] | | | 12.9%[f] | 15.1%[f] | | 8.5%[f] | 8.5%[f] | | |
| GERD | 1.9%[d] | 1.2%[d] | | 1.9%[d] | 1.2%[d] | 3.1%[d] | 3.1%[d] | | | | | | | | | |
| Gastroenteritis | | | | | | | | | | 1.2%[d] | 0.6%[d] | | | | | |
| Non-Upper GI | 18.2%[d] | 12.9%[d] | | 20.1%[d] | 18.4%[d] | 18.9%[d] | 19%[d] | | | | | | | | | |
| Diarrea | 5%[d] | 4.9%[d] | | 5%[d] | 6.7%[d] | 3.8%[d] | 6.7%[d] | | | 24.5%[f] | 21.4%[f] | | 10.0%[f] | 9.2%[f] | | |
| Infection | | | | | | | | | | 58.9%[abcdfh] | 58.5%[abcdfh] | | 47.7%[fh] | 46.2%[fh] | 54.6%[g] 58%[h] | 62.2%[g] 63%[h] |
| Severe Infection | | | | | | | | | | | | | | | 4.1%[g] | 8.2%[g] |
| Serious Infection | | | | | | | | | | 16.0%[ab cd] | 8.8%[abcd] | <0.05[abcd] | | | | |
| Pneumonia | | | | | | | | | | 4.9%[d] | 1.9%[d] | ns[d] | | | | |
| UTI/ Pyelonephritis / Urosepsis | | | | | | | | | | 5.5%[d] | 2.5%[d] | | | | | |
| CMV/ Pneumonia CMV | | | | | | | | | | 1.2%[d], 1.9%[f] | 0[d] , 1.8%[f] | | 0%[f] | 0.8%[f] | | |
| CMV infection | | | | | | | | | | 2%[h] | 2%[h] | | 1%[h] | 1%[h] | 1.0%[g] 2.0%[h] | 1.0%[gh] |
| Sepsis | | | | | | | | | | 0[d] | 1.3%[d] | | | | | |
| Upper Respiratory Infection | | | | | | | | | | 01.6%[d] | 1.3%[d] | | | | | |
| | | | | | | | | | | | | | | | | |
| Malignancies | | | | | | | | | | 2.4%[fh] | 3.1%[fh] | | 6.2%[fh] | 0.8%[fh] | 11%[h] | 4%[h] |
| Lymphomas | | | | | | | | | | 0.6%[fh] | 1.2%[f], #2[dh] | | 0[fh] | 1 relapse[fh] | 0[h] | 1%[h] |
| NonMelanoma Skin carcinoma | | | | | | | | | | Similar[d] , 1.8%[fh] | Similar[d], 1.2%[fh] | | 4.6%[fh] | 0[fh] | 6%[h] | 1%[h] |
| Other Malignancies | | | | | | | | | | Similar[d], 0[f] 1.2%[h] | Similar[d], 0.6%[fh] | | 2.3%[fh] | 0[fh] | 6%[h] | 2%[h] |
| Hematologic AEs | | | | | | | | | | | | | infrequent, comparable[f] | infrequent, comparable[f] | | |
| Anemia, Leukopenia, thrombocytopenia | | | | | | | | | | Similar[d] | Similar[d] | | | | | |
| Anemia | | | | | | | | | | | | | 2.3%[h] | 3.8%[h] | 3.1%[gh] | 8.2%[gh] |
| Leukopenia | | | | | | | | | | | | | 4.6%[h] | 3.8%[h] | 2.1%[g] 7.2%[h] | 7.1%[gh] |
| Neutropenia | | | | | | | | 0.6%[de#&] | 3.1%[de#&] | | | | 3.1%[h] | 0[h] | 0[g] 2.1%[h] | 1.0%[gh] |
| Thrombocytopenia | | | | | | | | | | | | | 0[h] | 0[h] | 0[h] | 1%[h] |

a:Neumayer 2002[56] b:Budde 2003[57] c:Budde 2003[58] d:Budde 2004[3] e: Budde 2004[60] f:Budde 2005[61] g:Budde 2004[59] h=Budde(2006)[62] #:*p* =ns[e] &: CI=-6.74 to 0.8[d]

*my*PROMS (*myfortic* PROSPECTIVE MULTICENTER STUDY)[63]

This trials involves an ongoing prospective open label, multicenter study. The primary objective is to assess patient and graft survival, incident of acute rejection, graft function, and specific safety parameters in both *de novo* and maintenance renal transplant patients receiving MPS and CsA with or without corticosteroids. Additional criteria are provided below in Table

| | |
|---|---|
| • Must use MPS and CsA with or without corticosteroids | • Levels of CsA must be assessed using $C_2$ monitoring and CsA dosing adjusted; according to C2 levels |
| • Studies involving maintenance renal transplant patients must receive MPS and CsA for 6 months | • Studies involving *de novo* renal transplant patients must continue for 12 months |
| • All studies must have the same visit schedule | |

Outcomes for the studies described below are summarized in table 3 at the end of this section with adverse events summarized in table 4.

All of the trials which compromise the myPROMS project demonstrate that a conversion of MMF to MPS does not adversely affect the outcomes of safety or efficacy. While the information provided by the ERL B302 Study Group is beneficial as the original design including blinding and randomization, the *my*PROMS adds to this by studying the outcome of patients given higher than equimolar dosages.

Table 3: myPROMS Study Group

| First Author | Study Type | Total (N) | Population Characteristics | Endpoints | MMF dose (mg /day) | Treatment History | Other meds | MPS (N) | MPS dose start | MPS: # decreased | MPS: # discontinued | (interruption, adjustment or dc) | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nashan[64] | Multicenter, open-label, single-arm trial (myPROMS ERL2045-DE02) | 57 | 65% male, 98% caucasian, cadaveric 77.2% | safety and tolerability, 3 mo interim analysis | 1000, 1500, 2000mg/d | 3m to 3y post: 3-6m (22%), 6-12m (16%), 1-3y (32%), 3-5y (16%), >5y (14%); | ME-CsA w/ or w/o steroids | 57 | 720, 1080 or 1440mg/day | 1.8% (GI AE) | | | 1 (1.8%) case of BPAR |
| Nashan[63] | Single-arm , multicenter, open-label. DE02 protocol | 57 | 77.2% cadaveric; 65% male; 25% second, 98% caucasian | safety and tolerability, 3mo interim (planned 200) | 500, 1000 ,1500, 2000mg/d | 3-6m (23%), 6-12m (16%), 1-3y (31%), 3-5y (16%), >5y (14%); | ME-CsA w/ or w/o steroids | 57 | 360, 720, 1080 or 1440mg/day | 1.8% (GI AE) | 1.8% (GI) | | 1.8% BPAR |
| | Citing LA01 protocol, Giron | 93 | 66.7% male, 52.7% caucasian, included children # unknown | safety and efficacy,3mo interim, | 91.1% on 2000mg /d | 2.2 ± 1.8 years post transplant | | | 720mg BID, all regardless of dose | 6patients | none | | none |
| Abbud-Filho[67] | Prospective, open label, multicenter, conversion to MPS: 90 day interim analysis (myProms-LA01) | 93 | 93 adults, 3 children, age 37.4±12.2, 67% male, 63% caucasian, 1% black | | 2000 except 8 on avg of 1250 | 3mo post transplantation | ME-CsA w/steroids | 93 | 720mg BID | | 0% | 6% | |
| Duro Garcia[66] | Multicenter, open-label, single-arm trial, conversion to MPS: 6mo | 237 | 39.1± 13.8yrs; 112 caucasian, 13 African American, 112 other; 19 children | | 2000 (64/237 on less, 1.22± 0.29g/day) | >3 mo post transplant | ME-CsA w/ or w/o steroids | 237 | 720mg BID | AEs: 10% (24), diarrhea (10), hyperbilirubinemia (4), leukopenia (4), anemia (1), hyperuricemia (1), Abdominal pain (2), Cholecystolithiasis (2); 11 of 64 converted to a higher dose were reduced | | | BPAR: #3, 0 graft loss, 1 motor vehicle accident |
| Massari[6] | Prospective, open label, multicenter, conversion to MPS: 6mo (myPROMS-LA01) | 237 | 218 adults, 59% male, 39.1± 13.8yrs, 2.6± 2.4yr post transplant | | 2000 (64/237 on less) | >3 mo post transplant | ME-CsA w/ or w/o steroids | 237 | 720mg BID | AEs: 10% (24), 7 of 74 converted to a higher dose were reduced, Hematological AEs: 2%, GI AE: 5% | | | |
| Massari[65] | Prospective, open label, multicenter 6mo (myPROMS) | 47 | subset of 237 from ref 91 and 29 | | 47/237 on 1400± 150mg/day | 3mo post transplantation | | 47 | 720mg BID | AEs: 15% (7) | 0% | | |
| Pietruck[68] | 63 sites throughout Asia-Pacific, Europe and Latin America (myPROMS) | 588 | 44± 14yrs, 64% male, mean transplant time 37± 36mo | | | mean 37+36m post | ME-CsA w/steroids | 588 | 64% started on 1440mg | 37 (6.3%) reductions, 11 (1.9%) interruptions | | | |
| Nashan[69] | Single-arm, multicenter, open-label DEO2 protocol | 226 | 50.1± 12.2 yrs, 67% male, 96% Caucasian | Frequency of adverse events , efficacy, BPAR, graft loss, death | 750 (n=2), 1000(n=54), 1500(n=56), 2000(n=113) or 2500(n=1) mg/day | >3mo post transplant | ME-CsA w/ or w/o steroids | 266 | 720, 1080, 1440, 2160mg BID | 11 (4.9%) due to AE | 21, 11 (4.9%) due to AE or 7 (3.1%) | | 2.2% (5) BPAR 0 graft loss 0 deaths |

| Table 4: myPROMS, adverse events | | |
|---|---|---|
| | EC-MPS at 3mo | EC-MPS 0-6 mo |
| Any AE | 61.4[ab], 40.9%[cd] | 59.9%[e] 57.4%[f] 74.3%[g] 67%[h] |
| Severe AE | | 5%[h] |
| Infection | 28.1% of all AE[ab], 28%[cd] | 37%[e] 29.8%[f] 33%[h] |
| Severe Infection | | 4%[h] |
| Hematologic Aes | 1.1%[c] | 4.8%[e] 6.4%[f] |
| Thrombocytopenia | 0[c] | |
| Leukopenia | 0[c] | |
| Neutropenia | 0[c] | |
| Any GI AE | 15.8%[ab], 19.4%[cd] | 22%[e] 29.7%[f] 23.5%[g] |
| Upper GI | 10.8% of any GI[cd] | 12.6%[e] 17%[f] |
| Diarrhea | 5.4%[cd] | 10.9%[e] 10.6%[f] 8.7%[g] |
| Nausea | | 3.4%[g] |
| Upper Abdominal Pain | | 3.1%[g] |

a=Nashan[64] b=Nashan[63] c=Nashan citing Giron[63] d=Abbud-Filho[67]
e=Duro-Garcia[66] f=Massari[65] g=Pietruck[68] h=Nashan (2006)[69]

## Efficacy

### Efficacy Measures

Many measures are used to demonstrate efficacy in the organ transplant population. They include and are not limited to:

- Patient survival
- Graft survival
- Graft rejection (preferably biopsy proven, though it could be based on clinical and laboratory criteria, sometimes labeled presumed rejection) which may be defined by the subcategories:
  - Acute rejection
  - Chronic rejection

### Summary of efficacy findings: Renal Transplantation

In addition to the trials describing conversion from MMF to MPS previously discussed (see Dosage Administration: Dosage conversion), several articles investigate the efficacy of MPS in *de novo* renal transplant patients. Many of these originate from a group called the ERL B301 Study Group. A meta analysis of the trials comprising the myPROMS project demonstrate a rate of treatment failure at 1.9% with no episodes of graft loss. Renal function remained atable and MPS was well toleratedwith GI adverse events occurring in 23.5% none necessitating discontinuation of MPS.

ERL B301 Study Group

Figure 3

This group conducted a phase III, double-blind, randomized, multicenter, parallel group, 12 month study to evaluate the therapeutic equivalence of MPS with MMF by comparison of efficacy failure at 6 months.[79] Patients included were 18 to 75 years of age who had received a first cadaveric, living-unrelated or living-related HLA-identical donor kidney transplant. Efficacy failure was defined as the incidence of BPAR, graft loss, death or loss to follow up. The intent to treat population comprised 423 patients (213 in the MPS group and 210 in the MMF group). Outcome data for this series is summarized in Table 5 at the end of this section.

In 2001 data from the primary time point for analysis of 6 months was published.[79] No significant difference in the incidence of efficacy failure was found (25.8% for MPS versus 26.2% for MMF). The percentage of patients reporting an adverse event was the same at 98.1% with no statistically significant differences in the number of infections reported, the number of serious infections or the number of GI adverse events. In their discussion of the data the authors noted the number of patients with panel reactive antibodies greater than or equal to 1% and prolonged cold ischemia times greater than 24 hours was borderline significantly higher in the MPS group ($P = 0.019$ and $P = 0.51$, respectively) which would place them at greater risk of BPAR, and indicated potentially greater efficacy with MPS.

At the completion of the 12 month study period patients were offered an opportunity to enter an open-label extension phase where all patients were provided MPS. The goal of the open-label phase was collection of long term safety data. A total of 247 patients continued, 122 initially randomized to MPS and 125 who converted to MPS from the MMF group.. In March of 2005 safety and outcomes data on the 122 patients who were initially randomized to MPS and continued in the open-label phase was published and compared to the MMF arm of two randomized studies (RAD B251 and RAD B201) for the same time period of 12 to 36 months. Thirty-two patients (26%) discontinued the study before the 24-month visit due to AEs (n=15), withdrawal of consent (n=4) lost to follow up (n=4), death (n=4) or graft loss (n=2). The incidence of adverse events was noted to be comparable. Nine patients (7.4%) experienced BPAR, graft loss or death. The authors concluded that a comparable safety profile of MPS to MMF was confirmed.

Table 5: ERL B301, outcomes

| | Year | StudyTime Frame (Months) | N | MMF (N) | MMF dose start (mg/day) | MMF dose finish mg(day | MMF: # discontinued | MMF: composite interruption, adjustment or d iscontinued | MPS (N) | MPS dose start | MPS dose finish | MPS: # discontinued | MPS; composite interruption, adjustment or discontinued | Clinical Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Salvadori[79] | 2001 | 6 | 423 | 210 | 1000mg BID | 90-100% of the planned nominal dose, no significant differences between the average daily dose | 18.10% | 17.6%, ns | 213 | 720mg BID | 90-100% of the planned nominal dose, no significant differences between the average daily dose | 21.60% | 13.1%, ns | MPS v MMF: Efficacy failure 25.8 v 26.2; BPAR 21.6 v 22.9; Graft loss 3.3 v 4.3; death 0.5 v 1.0; BPCR 3.8 v 5.7% |
| Salvadori[80] | 2002 | 12 | 423 | 210 | 1000mg BID | | | 19.5% due to GI AEs, ns | 213 | 720mg BID | | | 15% due to GI AEs, ns | BPAR, graft loss, death or loss to follow-up (MPS v MMF): 12mo=28.2% v 28.1% BPAR: 22.5% v 24.3% BPCR 3-12mo: 2.8% v 6.2% Death, graft loss: 4.7% v 6.7% |
| De Mattos[81] | 2002 | 12 | 423 | 210 | 1000mg BID | | | 19.5% due to GI AEs, ns | 213 | 720mg BID | | | 15% due to GI AEs, ns | BPAR, graft loss, death or loss to follow-up (MPS v MMF): 12mo=28.2% v 28.1% [95% CI 08.5, +8.6]. BPAR: 22.5% v 24.3%, p=ns BPCR 3-12mo: 2.8% v 6.2%, p=ns Death, graft loss: 4.7% v 6.7%p=ns |
| Salvadori[4] | 2004 | 12 | 423 | 210 | 1000mg BID | | 24.8% discontinued, 18.6% due to AEs, Lab abnormalities, graft loss or death, 13.8% to AEs, GI AEs 5.2%, Infections 3.3% | 0-12mo: 19.5% due to GI AEs, ns; 0-6mo: 17.1%, ns | 213 | 720mg BID | | 29.1% discontinued, 20.2% due to AEs, Lab abnormalities, graft loss or death, 16.9% to AEs, 4.7% to GI AEs, infection 2.3% | 0-12mo: 15.0% due to GI AEs, ns; 0-6mo: 13.1% due to GI AEs, ns | BPAR, graft loss, death or loss to follow-up (MPS v MMF): 6mo=25.8% v 26.2% [95% CI -8.7, +8.0], 12mo=28.6% v 28.1% [95% CI 08.0, +9.1]. BPAR, graft loss or death:12mo= 26.3% v 28.1% BPAR: 12mo=22.5 v 24.3 [95% CI -9.8, +6.3]' BPCR: 3-12mo=2.8 v 6.2, p=ns |
| Salvadori[82,83] | 2005 | 12-24, converted all to MPS | 125 | | | | | | 125 | 720mg BID | | | | BPAR 4.8%; graft loss 0.8% |
| Salvadori[82,83] | 2005 | 12-24, continued MPS | 122 | | | | | | 122 | 720mg BID | | | | BPAR 3.3%, Graft loss 1.6% |
| Salvadori[84] | 2005 | 12-36, patients continuing on MPS | 122 | | | | | | 122 | 720mg BID | | 32 (26%); 15 or 16 (13%) due to AE | | Efficacy 7.4%, BPAR 3.3%, Graft loss 1.6%, Death 3.3% |

Table 6: ERL B301 study group, adverse events

| | 0-6mo | | | 0-12mo | | | 12-36mo | |
|---|---|---|---|---|---|---|---|---|
| | MMF | MPS | *P* value | MMF | MPS | *P* value | EC-MPS | MMF-to EC-MPS |
| Any AE | 98.1%[a] | 98.1%[a] | | 98.1%[d] | 98.1%[d] | | 87.7%[g] 88%[h] | 89%[h] |
| severe AE | 38.6%[a] | 36.2%[a] | | 41%[d] | 38.0%[d] | | 29.5%[ef] 30%[h] | 27.2%[ef] 27%[h] |
| Serious AEs | 49.5%[a] | 52.6%[a] | | 53.8%[d] | 54.9%[d] | | 44%[h] | 42%[h] |
| Infection | 69.5%[a] | 66.7%[a] | | 73.3%[d] | 69.5%[d] | | 63.1%[efg] 63%[h] | 60.8%[ef] 61%[h] |
| Severe infection | 10.5%[a] | 7%[a] | | 12.4%[d] | 8.9%[d] | | 10.7%[ef] 11%[h] | 9.6%[ef] 10%[h] |
| Serious Infection | 24.3%[a] | 19.7%[a] | ns[a] | 27.1%[bcd] | 22.1%[bcd] | ns[bc] | | |
| Serious Pneumonia | | | | 4.3%[d] | 0.5%[d] | 0.01[d] | | |
| CMV infection | | | | 20.5%[d] | 21.6%[d] | | 5.7%[efg] 6%[h] | 0.8%[ef] 2%[h] |
| CMV disease | | | | 4.3%[d] | 4.7%[d] | | | |
| GI AEs | | | | 80.0%[d] | 80.8%[d] | ns[d] | | |
| Upper GI AEs | | | | 54.3%[d] | 53.5%[d] | | | |
| Lower GI AEs | | | | 68.1%[d] | 68.5%[d] | | | |
| Malignancies/Lymphoma | | | | 5 patients[d] | 5 patients[d] | | 9.0%[gh] | 6%[h] |
| Nonmelanoma skin carcinoma | | | | 3 pts[d] | 2 pts[d] | | 4.1%[g] 4%[h] | 2%[h] |
| Lymphoma | | | | | | | 2.5%[g] 2%[h] | 0[h] |
| Kaposi's sarcoma | | | | | | | 0[h] | 0[h] |
| other | | | | | | | 2.5%[g] 2%[h] | 3%[h] |
| Neutropenia | | | | similar[d] | similar[d] | | | |
| Anemia/leukopenia | | | | similar[d] | similar[d] | | | |
| Anemia | | | | | | | 9.8%[egf] | 8.0%[ef] |
| Leukopenia/Neutropenia | | | | | | | 5.7%[ef] | 2.4%[ef] |
| Leucopenia | | | | | | | 5.7%[g] | |
| Neutropenia | | | | | | | 0[g] | |
| Thrombocytopenia | | | | | | | 0[g] | |

a=Salvadori[79] b= Salvadori[80] c=De Mattos[81] d=Salvadori[4] e=Salvadori[82] f=Salvadori[83] g=Salvadori[84] h=Salvadori[85]

*my*PROMS (*myfortic* PROSPECTIVE MULTICENTER STUDY)

The *my*PROMS group previously described in this work has also presented data on the use of MPS in *de novo* renal transplant recipients in a 12 month, open-label, single-arm, multicenter, prospective study of patients on CsA with or without corticosteroids.[53] A total of 140 patients were enrolled and started on 720mg BID of MPS within 48 hours post reperfusion of the kidney. Efficacy is summarized in the following table.

| | 6mo | 12mo |
|---|---|---|
| Treatment failure (defined as BPAR, graft loss or death ) | 26 (18.6%) | 31 (22.1%) |
| BPAR | 22 (15.7%) | 27 (19.3%) |
| Graft loss | 2 (1.4%) | 3 (2.1%) |
| Death | 5 (3.5%) | 6 (4.2%) |
| Loss to follow-up | 1 (0.7%) | 1 (0.7%) |

Recently Schiavelli et al [88] reported data from a study that aimed to describe the short-term (3 month) outcome of *de novo* renal transplants at high risk for delayed graph function (DGF). Forty-six *de novo* renal transplant recipients were recruited and DGF developed in 58%. BPAR occurred in 7 (15%), graft loss in 3 and death in 2. All patients experienced at least one AE. AEs were cited as the cause of dosage adjustments in 9 cases while there were no discontinuations of MPS.

**Summary of efficacy findings: Liver Transplantation**

Standard primary immunosuppressive therapy after organ transplantation based on a CNI.[90] The use of MMF has reduced the incidence of acute rejection without renal toxicity in liver transplantation.[91,92,93,94] Several studies have shown the efficacy of MMF to improve CNI-induced nephrotoxicity, blood pressure and hyperuricemia in liver transplant patients with concomitant reduction or withdrawal of CNI.[95] In addition to the efficacy measures noted at the beginning of this section, measuring renal function is a component of establishing efficacy in liver transplant recipients.

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In a single-center study evaluated the use of MPS as a primary immunosuppressant or as a replacement for MMF in 90 liver transplant patients.[97] MPS was started at a median of 30 months post transplant. Mean age was 52.39 ± 11.08 years, 63% were men and then main indication for liver transplant was hepatitis C virus-induced cirrhosis. Mean administered daily dose was 720mg/day. Replacement of MMF occurred in 74.4%, while 12.2% were started on MPS due to loss of renal function, and 11.1% to treat an ACR. The results do not distinguish between those converting from MMF and those being initiated to mycophenolate. A GI AE was reported by 25 patients, abdominal pain (16.6%), and diarrhea (14.5%). MPS was discontinued in 2 patients while 6 required dose reduction. In the results serum low-density lipoprotein (LDL) cholesterol and triglyceride levels were significantly lower among patients on MPS than on MMF though data was not offered. In their conclusion the authors noted the addition of MPS allowed for faster reduction in dose and serum levels of CNIs without increasing ACR though no data is offered to support this.

Zanotelli et al[99] describe 100 patients in a single-arm cohort who were on or added MPS to their immunosuppressive regimen. MPS was started at a median of 21 months after liver transplant and the median dose of MPS administered was 720 mg. Adverse events, MPS discontinuation or reduction and renal function were monitored at 6 months and one year. The authors concluded that MPS in liver transplant have efficacy and safety as a primary immunosuppressant or in replacement of MMF.

A retrospective analysis of 47 patients initiated on MPS for ≥ 3 months noted a starting dose of 720mg/day.[101] At 3 months the average dose was 783 ± 440mg/day and at 6 months 568 ± 460mg/day. The onset of GI symptoms was within an average of 28 days post MPS initiation. Ten (28%) patients had BPAR at 3 months.

### Summary of efficacy findings: Heart Transplantation

At the May 2004 American Transplant Congress, Kobashigawa et al [105] reported the preliminary 6 month results of 154 *de novo* primary heart transplant recipients. In this single-blind, multicenter trial, patients were randomized to MPS 1080mg BID or MMF 1500mg BID. The primary study objective was to investigate the incidence of treatment failure: biopsied and treated acute rejection, graft loss or death during the first 6 months. The secondary objective was to investigate overall safety and tolerability. Treatment failure occurred in 48.7% versus 51.3% while the incidence of BPAR was 30.8% and 27.6%, for MPS and MMF, respectively. AEs occurred in 100% of the MPS group and 97% of the MMF.

Six month results of this study (noted as the CERL1080A2401 study group) were also published in an abstract presented at the XX International Congress of the Transplantation Society.[106] Results of the primary efficacy variable of treatment failure (treated biopsy proven acute rejection, graft loss or death) was 50.0% for MPS and 51.3% for MMF (95% CI -17.1 to 14.5) and considered non-inferior based on a 15% upper confidence limit. Death was 3.8% versus 5.3% for MPS and MMF. The authors concluded that MPS was therapeutically similar to MMF.

In 2006, complete 12 months results of the ERL2401 Heart Study Investigators was published.[5] This article provided details in addition to those published in the abstract including the E randomization to MPS 1080mg BID (n=78) or MMF 1500mg BID (n= 76).efficacy was analyzed in the intent-to-treat population and safety in the safety population (no further definition offered). A new non-inferiority margin of 10% was chosen. Treatment failure at 6 months, was similar for both treatments: 52.6% for EC-MPS and 57.9% for MMF (2-sided 95% confidence interval [CI]: -21.0% to 10.4%). At 12 months, treatment failure was 57.7% for EC-MPS and 60.5% for MMF (2-sided 95% CI: -18.4 to 12.7), and death and graft loss rate was 5.1% vs. 9.2% for EC-MPS and MMF at 12 months, respectively (2-sided 95% CI: -12.2 to 4.1). The overall incidence of AEs at 12 months was comparable between study groups, with any difference failing to reach statistical significance. In a subset of 32 patients pharmacokinetic evaluations were performed. Data was only included if patients completed all plasma concentration profiles throughout the 12 hour dosage interval. AUC and $C_{max}$ were normalized to MPS 1080mg and MMF 1500mg dosages. PK data may be reviewed in the Pharmacokinetic section of this document. The authors concluded that MPS and MMF have comparable efficacy, safety and tolerability profiles in the first year after heart transplantation. Compiled outcomes are available in the following table.

Heart Transplant Outcomes

| Author | Year | MMF dose finish (mg/day) | MMF: # decreased | MMF: # discontinued | MPS dose finish (mg/day) | MPS: # decreased | MPS: # discontinued | Treatment failure= BPAR, graft loss, or death | BPAR | death |
|---|---|---|---|---|---|---|---|---|---|---|
| **Kobashigawa[105]** | 2004 | | | | | | | 48.7%MPS 51.3% MMF (diff – 2.6, 95% CI -18.4, 13.2) | 30.8% MPS 27.6% MMF | 3.8% MPS v 5.3% MMF |
| **Gambino[106]** | 2004 | | | | | | | 50% MPS 51.3% MMF (diff -1.3, 95% CI -17.1 to 14.5) | | 3.8% MPS v 5.3% MMF |
| **Kobashigawa[5]** | 2006 | Avg daily dose in percent of the nominal dose was 79.0% (p=0.015). T | Two or more dose reductions: MMF 42.1% v EC-MPS 26.9%, p=0.048 | 19.7%, due to AEs 9.2% | Avg daily dose in percent of the nominal dose was 88.4%, p=0.015. | Two or more dose reductions: MMF 42.1% v EC-MPS 26.9%, p=0.048 | 21.8%, due to AEs 15.4% | 6mo: 52.6% MPS 57.9% MMF CI -21.0% to 10.4%; 12mo 57.7% v 60.5% CI -18.4 to 12.7 | 70.5% MPS v 68.4% MMF, CI -12.5 to 16.6 | 5.1% MPS 9.2 % MMF CI -12.2 to 4.1 |

## Adverse Events (Safety Data)

As previously noted adverse events (AEs), especially gastrointestinal AEs, have been demonstrated to impact efficacy and costs. In addition to the rate of AEs reported in the various clinical trials data has been published on other efforts to assess rates of side effects, as well as, establish its impact on quality of life.

### Common Adverse Events

As the dosage regimen for MMF and MPS varies with each type of organ transplanted a subsection is devoted to each.

*Renal:*

With a plethora of studies citing the incidence of various AEs in a number of different study types, it becomes necessary to presents AE results in similar groups as noted in the table below.

| | *De novo* renal transplant | Maintenance renal transplant converted from MMF to MPS |
|---|---|---|
| Single-arm study | AE Table 1 | AE Table 2 |
| Comparative trial | AE Table 3 | AE Table 4 |

**AE Table 1: *De novo*, single-arm MPS studies**

| | 0-14days | Initial 0-3mo | Final 3-6mo | 0-6mo | 0-12mo | 12-36mo |
|---|---|---|---|---|---|---|
| Any AE | | 100%[e] | | | 77.9%[d] | 87.7%[f] 88%[h] 89%[o] |
| Serious AEs | 41.6%[g] | 29%[e] | | | | 44%[h] |
| Severe AEs | 25.0%[g] | | | | | 29.5%[bc] 30%[h] |
| Infection | | | | | 60.7%[d] | 63.1%[bcf] 61%[o] |
| Serious Infection | | | | | 58.6%[d] | |
| Severe infection | | | | | | 10.7%[bc] 11%[h] |
| UTI | | 28%[e] 16.6%[hm] | | 26.0%[jk] | 27.1%[d] | |
| Pneumonia, bacterial | | 2%[e] | | | | |
| Bacterial | | | | | 28.6%[d] | |
| Viral | | | | | 24.3%[d] | |
| Cytomegalovirus | | 7%[e] 8.3%[hm] | | 10.8%[jk] | 12.1%[d] | 5.7%[bcf] 6%[h] |
| Herpes Simplex | | | | 7.3%[jk] | 10%[d] | |
| Fungal | | | | | 5.7%[d] | |
| Hypercholesteremia | | | | | 12.1%[d] | |
| hyperlipidemia | | | | | 9.3%[d] | |
| Hypertension | | | | | 9.3%[d] | |
| Diabetes | | | | | 2.9%[d] | |
| Lymphocele | | | | | 5.7%[d] | |
| Blood and lymphatic system disorders | | | | | 20.7%[d] | |
| Neutropenia | | | | | 9.4%[d] | 0[f] |
| Leukopenia | | | | 13.8%[k] | 4.3%[d] | 5.7% |
| Anemia | | 13%[e] | | 27.1%[jk] | 7.9%[d] | 9.8%[bc] |
| Thrombocytopenia | | 2%[e] | | | | 0[f] |
| Leukopenia/Neutropenia | | | | | | 5.7%[bc] |
| Malignancies | | | | | 2.0%[p] | 9.0%[fh] |
| lymphoma | | | | | 0[d] 1.0%[p] | 2.5%[f] 2%[h] |
| Nonmelanoma skin carcinoma | | | | | | 4.1%[f] 4%[h] |
| Kaposi's sarcoma | | | | | | 0[h] |
| Leukemia | | | | | 0.5%[p] | |
| Lung carcinoma | | | | | 0.5%[p] | |
| Other | | | | | | 2.5%[f] 2%[h] |
| GI AEs | | | | | 35%[d] | |
| Diarrhea | | 7%[e] 16.6%[hm] | | | 12.9%[d] | |
| Constipation | | | | 35.5%[jk] | 11.4%[d] | |
| Nausea | | 9%[a] | 0%[a] | | 4.3%[d] | |
| Vomiting | | 4.5%[a] | 0%[a] | | 0.7%[d] | |
| Nausea and vomiting | | 15%[e] | | | | |
| Abdominal pain | | 28%[e] | | | | |
| Dyspepsia | | 27%[a] | 14%[a] | | | |
| Acid regurgitation | | 18.2%[a] | 9%[a] | | | |
| Epigastralgia | | 9%[a] | 4.5%[a] | | | |
| Poor appetite | | 4.5%[a] | 9%[a] | | | |

a=Chang(2005)[109] b=Salvadori(2004)[82] c=Salvadori(2005)[83] d= Vogt[54] e=Schiavelli(2006)[88] f=Salvadori(2005)[84] g=Kaplan(2005)[110] h=Sumethkul[35] j=Rostaing (2004)[111] k=Rostaing (2004)[112] m=Sumethkul (2004)[113] o=Salvadori (2006)[85] p=Rostaing (2006)[55]

**AE Table 2: Single-arm conversion studies**

| | EC-MPS at 3mo | EC-MPS 0-6 mo | MPS 0-12 mo | MPS 12-24 mo | MPS 0-24 mo |
|---|---|---|---|---|---|
| **Any AE** | 61.4[ab], 40.9%[cd] | 59.9%[ek] 57.4%[f]<br>74.3%[g] 67%[o] | 86.9%[h] 87%[s] | | 89%[r] 92%[s] |
| **Severe AE** | | 5%[o] | 20%[s] | 29.9%[j] | 27.2%[pq] 27%[r] |
| **Serious AE** | | | | | 42%[r] |
| | 28.1% of all AE[ab] | 37%[ek] 29.8%[f] | | | 60.8% [pq] 61%[r] |
| **Infection** | 28%[cd] | 33%[o] | 47.7% [h] 48%[s] | 54.6% [j] | 58% [s] |
| **Serious Infection** | | | | 4.1% [j] | |
| **Severe Infection** | | 4%[o] | | | 9.6%[pq] 10%[r] |
| **CMV** | | | 1%[s] | | 0.8% [pq] 2%[rs] |
| **CMV/Pneumonia CMV** | | | 0% [h] | | |
| **Hematologic AEs** | 1.1%[c] | 4.8%[ek] 6.4%[f] | Infrequent [h] | | |
| **Thrombocytopenia** | 0[c] | | 0[s] | | 0.8%[r] 0[s] |
| | | | | | 8.0% [pq] 5.6%[r] |
| **Anemia** | | 2.1%[k] | 2.3%[s] | 3.1% [j] | 3.1% [s] |
| **Leukopenia** | 0[c] | 2.1%[k] | 4.6%[s] | 2.1% [j] | 10.4%[r] 3.8%[s] |
| **Neutropenia** | 0[c] | | 3.1%[s] | 0 [j] | 0%[r] 2.1%[s] |
| **Leukopenia/Thrombocytopenia** | | | | | 2.4% [pq] |
| | 15.8%[ab], 19.4%[cd], | 22%[ek] 29.7%[f] | | | |
| **Any GI AE** | 15.8%[m] | 23.5%[g] | 44.6% [h] | | |
| | | 10.9%[ek] 10.6%[f] | | | |
| **Diarrhea** | 5.4% [cd , 46%] | 8.7%[g] | 10.0% [h] | | |
| **Constipation** | 35%[m] | | | | |
| **Serious GI AE** | | | 6.2% [h] | | |
| **Upper GI** | 10.8% of any GI[cd] | 12.6%[ek] 17%[f] | | | |
| **Nausea** | | 3.4%[g] | 6.9% [h] | | |
| **Vomiting** | | | 8.5% [h] | | |
| **Abdominal pain** | 45%[m] | | | | |
| **Upper Abdominal Pain** | | 3.1%[g] | | | |
| **Dyspepsia / Indigestion** | 42%[m] | | 6.9% [h] | | |
| **Reflux** | 38%[m] | | | | |
| **Malignancies** | | | 6.2% [h] 6%[s] | | 6%[r] 11%[s] |
| **Lymphomas** | | 0[k] | 0 [hs] | | 0[rs] |
| **Non-melanoma skin cancer** | | 0.8%[k] | 4.6% [h] 5%[s] | | 2%[r] 6%[s] |
| **Kaposi's sarcoma** | | | | | 0[r] |
| **Other malignancies** | | | 2.3% [h] 2%[s] | | 3%[r] 0[s] |

a=Nashan(2004)[64] b=Nashan(2004)[63] c=Nashan citing Giron(2004)[63] d=Abbud-Filho(2004)[67] e=Duro-Garcia(2004)[66] f=Massari(2004)[65] g=Pietruck(2005)[68] h=Budde(2005)[61] j=Budde[59] k=Massari[6] m=Calvo (2006)[114] o=Nashan (2006)[69] p=Salvadori(2004)[82] q=Salvadori(2005)[83] r=Salvadori (2006)[85] s=Budde (2006)[62]

| **AE Table 3: Comparative *de novo* studies** | **0-6mo** | | | **0-12mo** | | | **12.6±8.5mo** | **11.6±7.0mo** | ***p* value** | **12-36mo** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **MMF** | **MPS** | ***p* value** | **MMF** | **MPS** | ***p* value** | **MMF** | **MPS** | | |
| **Any AE** | 98.1%[a] | 98.1% [a] | | 98.1%[d] | 98.1% [d] | | | | | 88%[f] |
| **severe AE** | 38.6% [a] | 36.2% [a] | | 41% [d] | 38.0% [d] | | | | | 30%[f] |
| **Serious AEs** | 49.5% [a] | 52.6% [a] | | 53.8% [d] | 54.9% [d] | | | | | 44%[f] |
| **Infection** | 69.5% [a] | 66.7% [a] | | 73.3% [d] | 69.5% [d] | | | | | 63%[f] |
| **Severe infection** | 10.5% [a] | 7% [a] | | 12.4% [d] | 8.9% [d] | | | | | 11%[f] |
| **Serious Infection** | 24.3% [a] | 19.7% [a] | ns | 27.1% [bcd] | 22.1% [bcd] | ns[bc] | | | | |
| **Life threatening infection** | | | | | | | 7.5%[g] | 8.5%[g] | ns[g] | |
| **Serious Pneumonia** | | | | 4.3% [d] | 0.5% [d] | 0.01 [d] | | | | |
| **CMV infection** | | | | 20.5% [d] | 21.6% [d] | | 9.61%[g] | 10.1%g | ns[g] | 6%[f] |
| **CMV disease** | | | | 4.3% [d] | 4.7% [d] | | 9.4%[g] | 10.2%[g] | ns[g] | |
| **Minor infections (wound infection/fungal/UTI)** | | | | | | | | | | |
| **GI AEs** | | | | 80.0% [d] 33.3%[e] | 80.8% [d] 32.4%[e] | ns [de] | 18.9%[g] | 20.3%[g] | ns[g] | |
| **Upper GI AEs** | | | | 54.3% [d] 11.8%[e] | 53.5% [d] 18.9%[e] | ns[e] | | | | |
| **Nausea** | | | | 4.3%[e] | 2.7% [e] | ns [e] | | | | |
| **Vomiting** | | | | 1.07% [e] | 2.7%[e] | ns [e] | | | | |
| **Upper abdominal pain** | | | | 2.7% [e] | 13.5%[e] | ns [e] | | | | |
| **Gastric distention** | | | | 2.15%[e] | 0 [e] | ns [e] | | | | |
| **Mild UGI symptoms controlled by RX** | | | | | | | 18.9%[g] | 15.2%[g] | ns[g] | |
| **Lower GI AEs** | | | | 68.1% [d] | 68.5% [d] | | | | | |
| **Diarrhea** | | | | 19.3%[e] | 13.5%[e] | ns[e] | | | | |
| **Malignancies/Lymphoma** | | | | 5pts [d] | 5pts [d] | | | | | 9%[f] |
| **Nonmelanoma skin carcinoma** | | | | 3 pts [d] | 2 pts [d] | | | | | 4%[f] |
| **Lymphoma** | | | | | | | | | | 2%[f] |
| **Kaposi's sarcoma** | | | | | | | | | | 0[f] |
| **Other** | | | | | | | | | | 2%[f] |
| **Hematological** | | | | | | | 9.4%[g] | 5.1%[g] | ns[g] | |
| **Anemia/Leukopenia** | | | | similar [d] | similar [d] | | | | | |
| **Anemia** | | | | | | | | | | 7.4%[f] |
| **Leukopenia** | | | | | | | | | | 13.9%[f] |
| **Neutropenia** | | | | similar [d] | similar [d] | | | | | 2.5%[f] |
| **Thrombocytopenia** | | | | | | | | | | 0.8%[f] |
| a=Salvadori[79] b= Salvadori[80] c=De Mattos[81] d=Salvadori[4] e =Kamar (2005)[107] f=Salvadori (2006)[85] g=Minz(2006)[86] | | | | | | | | | | |

AE Table 4: Comparative maintenance (>90days) studies

| | At 3months | | | At 6months | | At 12months | | 0-48 hours | | 0-3months | | 0-12months | | | | 12-36mo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MPS | MMF | *P* value | MPS | MMF | MPS | MMF | MPS | MMF | MPS | MMF | MPS | MMF | *P* value | 12-24mo | MPS |
| Any AE | | | | | | | | | | | | 93.7%[abcdh] | 92.6%[abcd] | ns[abd] | 88.5%[h]<br>89%[j] | 92%j |
| Severe AEs | | | | | | | | | | | | | | | 19%[j] | 29.6%[g]<br>32%[j] |
| Serious AEs | | | | | | | | | | | | 23.3[abcd] | 30.1[abcd] | ns[abcd] | | |
| Dizziness | | | | | | | | 4.1%[f] | | | | | | | | |
| Flushing | | | | | | | | 4.1%[f] | | | | | | | | |
| Orthostatic hypotension | | | | | | | | | 8.3%[f] | | | | | | | |
| Headache | | | | | | | | | 8.3%[f] | | | | | | | |
| Any GI | 26.4%[de] | 20.9%[de] | ns[d] | 28.9%[de] | 27.6%[de] | 29.6%[d] | 24.5%[d] | | | | | 60.0[abc]<br>60.4%[d]<br>56.6[h] | 61.0%[abc],<br>61.3%[d]<br>57.1[h] | ns[abd] | 49.2%[h] | |
| Serious GI AEs | | | | | | | | | | | | 3.8%[jh] | 4.9%[h] | | 4.6%[h] | |
| Upper GI | 13.2%[de] | 13.5%[de] | | 15.7%[de] | 16.6%[de] | 15.1%[d] | 14.1%[d] | | | | | | | | | |
| Dyspepsia | 3.1%[d] | 3.1%[d] | | 5.7%[d] | 2.5%[d] | 3.8%[d] | 3.7%[d] | | | | | 13.8%[h] | 14.7%[h] | | 49.2%[h] | |
| Nausea | 6.3%[d] | 3.7%[d] | | 8.2%[d] | 7.4%[d] | 5.7%[d] | 5.5%[d] | 4.1%[f] | | | | 24.5%[h] | 19.0%[h] | | 8.5%[h] | |
| Vomiting | 0.6%[d] | 0.6%[d] | | 3.8%[d] | 4.9%[d] | 1.9%[d] | 3.7%[d] | | | | | 15.1%[h] | 12.9%[h] | | 8.5%[h] | |
| GERD | 1.9%[d] | 1.2%[d] | | 1.9%[d] | 1.2%[d] | 3.1%[d] | 3.1%[d] | | | | | | | | | |
| Gastroenteritis | | | | | | | | | | | | 0.6%[d] | 1.2%[d] | | | |
| Non-Upper GI | 18.2%[d] | 12.9%[d] | | 20.1%[d] | 18.4%[d] | 18.9%[d] | 19%[d] | | | | | | | | | |
| Diarrea | 5%[d] | 4.9%[d] | | 5%[d] | 6.7%[d] | 3.8%[d] | 6.7%[d] | | 4.1%[f] | | | 21.4%[h] | 24.5%[h] | | 9.2%[h] | |
| Infection | | | | | | | | | | | | 58.5%[abcdh] | 58.9%[abcdh] | | 46.2%[h] 46%[J] | 62.2%[g]<br>63%[j] |
| Severe Infection | | | | | | | | | | | | | | | | 8.2%[g] |
| Serious Infection | | | | | | | | | | | | 8.8%[abcd] | 16.0%[abcd] | <0.05[abcd] | | |
| Pneumonia | | | | | | | | | | | | 1.9%[d] | 4.9%[d] | ns[d] | | |
| UTI/ Pyelonephritis / Urosepsis | | | | | | | | 4.1%[f] | | | | 2.5%[d] | 5.5%[d] | | | |
| CMV/<br>Pneumonia CMV | | | | | | | | | | | | 0[d]<br>1.8%[h] | 1.2%[d]<br>1.9%[h] | | 0.8%[h] | |
| CMV infection | | | | | | | | | | | | | | | | 1.0%[gl] |
| Sepsis | | | | | | | | | | | | 1.3%[d] | 0[d] | | 1%[j] | |
| Upper Respiratory Infection | | | | | | | | | | | | 1.3%[d] | 01.6%[d] | | | |
| | | | | | | | | | | | | | | | | |
| Malignancies | | | | | | | | | | | | 3.1%h | 2.4%h | | 0.8%[h] 1%[j] | 4%j |
| Lymphomas | | | | | | | | | | | | #2[d]<br>1.2%[h] | 0.6%[h] | | 1 relapse[h]<br>1%[j] | 1%j |
| NonMelanoma Skin carcinoma | | | | | | | | | | | | Similar[d]<br>1.2%[h] | Similar[d]<br>1.8%[h] | | 0[hj] | 1%j |
| Other Malignancies | | | | | | | | | | | | Similar[d]<br>0.6%[h] | Similar[d]<br>0[h] | | 0[hj] | 2%j |
| Hematologic AEs | | | | | | | | | | | | | | | infrequent[h] | |
| Anemia, Leukopenia, thrombocytopenia | | | | | | | | | | | | Similar[d] | Similar[d] | | 0[j] | |
| Thrombocytopenia | | | | | | | | | | | | | | | | 1%j |
| Anemia | | | | | | | | | | | | | | | 3.8%[j] | 8.2%[g]<br>8.2%[j] |
| Leukopenia | | | | | | | | | | | | | | | 3.8%[j] | 7.1%[gl] |
| Neutropenia | | | | | | | | | | 0.6%[de#&] | 3.1%[de#&] | | | | 0[j] | 1.0%[gl] |

a:Neumayer 2002[56] b:Budde 2003[57] c:Budde 2003[58] d:Ref#3 e:Budde 2004[60] f: Arns[7] g= Budde[59] h=Budde (2005)[61] j=Budde (2006)[62] #: *p* =ns[e] &: CI=-6.74 to 0.8[d]

Due to the use of higher daily doses of 3000mg MMF and 2160mg MPS for heart transplantation, and lower daily doses of 1000mg MMF and 720mg MPS for liver transplantations, the incidence of AEs have been listed separately for each.

*Liver transplantation:*

| | 6mo median | 0-6mo | 0-12mo | 6-36mo |
|---|---|---|---|---|
| Total number of subjects with AEs | 40%a | | | |
| Infections and infestations | | 48.90%[b] | | |
| Fungal infection | | | 1.1%[d] | |
| Bacteria infection | | | 10%[d] | |
| Gastrointestinal disorders | | 79%[b] | 27.8%[d] 25%[c] | |
| Nausea | | 16%[b] | 5.6%[d] | 13.9%[e] |
| Diarrhea | 30%[a] | 24%b | 14.5%[d] 13%[c] | 16.6%[e] |
| Vomiting | | | 4.4%[d] | 0[e] |
| Gastritis | | 16%[b] | | |
| Dyspepsia | | | | 2.8%[e] |
| Abdominal distension | | | 11%c | 11.1%[e] |
| Abdominal pain | | | 16.6%[d] | 13.9%[e] |
| Anorexia | | | 4.4%[d] | |
| Anemia | | | 3.3%[d] 2%[c] | |
| Leukopenia | | | 1.1%[d] 4%[c] | |
| Anemia/ thrombocytopenia | 11%[a] | | | |

a = Villamil[115] b = Hsaiky[101] c = Zanotelli[99] d = Cantisani[97] e = Dumortier[90]

*Heart transplantation AEs:*

| Heart Transplant AEs | 6mo[a] | | | 12mo[b] | | |
|---|---|---|---|---|---|---|
| | EC-MPS | MMF | *P* value | EC-MPS | MMF | *P* value |
| Total number of subjects with AEs | 100% | 97% | ns | 100.0% | 98.7% | |
| Total number of subjects with AEs suspected to be drug related | | | | 55.1% | 55.3% | |
| Infections and infestations | 65% | 63% | ns | 73.1% | 65.8% | |
| Severe infection | | | | 3.8% | 3.9% | |
| CMV | | | | 16.7% | 13.2% | |
| Gastrointestinal disorders | | | | 69.2% | 61.8% | |
| Metabolism and nutrition disorders | | | | 64.1% | 65.8% | |
| Vascular disorders | | | | 60.3% | 68.4% | |
| Blood and lymphatic system disorders | | | | 56.4% | 55.3% | |
| Thrombocytopenia | | | | 3.8% | 9.2% | 0.177 |
| Nervous system disorders | | | | 52.6% | 52.6% | |
| Musculoskeletal and connective tissue disorders | | | | 47.4% | 38.2% | |
| Cardiac disorders | | | | 43.6% | 43.4% | |
| Respiratory, thoracic and mediastinal disorders | | | | 43.6% | 50.0% | |
| Psychiatric disorders | | | | 42.3% | 35.5% | |
| Renal and urinary disorders | | | | 33.3% | 38.2% | |
| Skin and sub-cutaneous tissue disorders | | | | 26.9% | 28.9% | |
| Eye disorders | | | | 12.8% | 6.6% | |
| Reproductive system and breast disorders | | | | 11.5% | 3.9% | |
| Hepatobiliary disorders | | | | 9.0% | 7.9% | |
| Endocrine disorders | | | | 6.4% | 10.5% | |
| Neoplasms benign, malignant and unspecified | | | | 6.4% | 2.6% | |
| Ear and labyrinth disorders | | | | 2.6% | 5.3% | |

a = Kobashigawa[105] b= Kobashigawa[5]

### Tolerability: Dosage Interruption, Reduction or Discontinuation

A large number of studies outline adverse event data with a great deal of focus on GI adverse events. The three randomized, double-blind, multicenter, controlled trials in renal transplantation[73,74,75] demonstrated that MMF is better tolerated than AZA.[2] Despite this there remains a high incidence of GI complications in renal transplant recipients taking MMF and patients with GI adverse events are more likely to undergo MMF dose reduction, interruption or discontinuation. Such complications may increase the risk of graft failure and therefore may potentially lead to higher transplantation costs.[19]

The cost associated with GI adverse events and subsequent reductions and discontinuations has been analyzed. Budde et al[60] cited Ferguson et al's abstract at the European Society for Organ Transplantation in 2003. This retrospective study of 772 records showed 49.7% of patients experiencing GI side effects. Nearly 40% underwent dosage adjustment or discontinuation. The incremental cost was US $3154 per patient during the first six months post transplant.

Changes in costs and graft survival between patients with no GI AEs remaining on MMF, having GI AEs but remaining on MMF, no GI AEs but still having to discontinue MMF and having GI AEs and having to discontinue MMF. The authors concluded that GI complications were costly, adding $6,000 to $8,000 to cost after transplantation. Complete data was published by Hardinger et al in 2004[120]. In the first post-transplantation year, GI complications were diagnosed in 1,753 patients (27.3%), and MMF was discontinued in 1,117 patients (17.5%). The frequency of MMF discontinuation was significantly higher in patients with GI complications (21.3%) than in those without such complications (16.0%) (odds ratio 1.33; $P < 0.0001$). Four- year graft survival was highest (87.1%) in patients who did not develop GI complications or discontinue MMF. The occurrence of GI complications in the first year was associated with significantly reduced graft survival after 12 months post-transplantation, the reduction being most pronounced when MMF was also discontinue (70.2%; $P<0.0001$) even when MMF was continued, GI complications were associated with lowered survival, to 83.0% ($P=0.0010$).

The two tables below are a compilation of incident rates of discontinuation, reduction, interruption or combination stratified by study time frame and broken down by cause when noted by the authors. The first table represents studies in *de novo* transplant recipients while the second is taken from studies converting patients from MMF to MPS.

Discontinuations, Reductions, Interruptions and the combination in *de novo* transplant recipients

| *De novo* | 0-6mo | | 0-12 | | 12-24 | | 12-36 | |
|---|---|---|---|---|---|---|---|---|
| | MMF | EPS | MMF | EPS | EPS Long Term | Newly converted | EPS Long Term | Newly converted |
| All Discontinuations, interruptions, reductions | | | | | | | | |
| GI | | | 19.5%[df] | 15% [df] | | | | |
| All Discontinuations | 18.1%[a] | 21.6%[a], 20.7%[c] | 24.8%[e] | 29.1% [e],10% [g], 0%[h],24.6% [c] | | | 26%[j] | |
| AE | | | 13.8% [e] | 16.9%[e], 7.1% [g],21.3% [c] | | | 15% [j], 12%[k] | |
| Infection | | | 3.3% [e] | 2.3% [e],10% [c] | | | | |
| Leukopenia | | | | 17% [c] | | | | |
| All Interruption | | | | 10% [g],12.8% [c] | | | | |
| AE | | | | 9.3% [g] | | | | |
| CMV | | | | 2.1% [g] | | | | |
| GI | | | | 2.1% [g],4.6% [c] | | | | |
| Hepatotoxicity | | | | 1.4% [g] | | | | |
| Leukopenia | | | | 1.4% [g],7.1% [c] | | | | |
| All Reduction | 41.7%[b] | 30.4% [b] | | 26.4% [g],19.7% [c] | | | | |
| Infection | | | | 8.7% [h] | | | | |
| CMV | | | | 2.9% [g] ,2.5% [c] | | | | |
| Hepatotoxicity | | | | 2.1% [g] | | | | |
| GI | | | | 4.3% [g],6.7% [h],4.6% [c] | | | | |
| Hematological | | | 2.1% [h] | | | | | |
| Leukopenia | | | 2.1%[g] | 7.6% [c] | | | | |

a=Salvadori (2001)[79] b= Budde (2006)[122] c=Rostaing(2006)[55] d=Salvadori(2002)[80] e= Salvadori(2004)[4] f=de Mattos(2002)[81] g=Vogt(2006)[54] h=Shiavelli(2006)[88] j=Salvadori(2005)[84] k=Salvadori(2006)[85]

| Discontinuations, Reductions, Interruptions and the combination in transplant recipients converted from MMF to MPS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Conversions** | **0-3mo** | | **0-6mo** | | **0-12mo** | | **12-24mo** | | **12-36mo** | |
| | **MMF** | **MPS** | **MMF** | **MPS** | **MMF** | **MPS** | **MPS Long Term** | **Newly converted** | **MPS Long Term** | **Newly converted** |
| **All Discontinuations, interruptions, reductions** | | 6%[a] | | | | | 8%[n] | 11%[n] | | |
| **GI** | | | | | 6.1%[k] | 8.2%[k] | | | | |
| **Upper GI AE** | | | | | 5.5%[k] | 4.4%[k] | | | | |
| **Diarrhea** | | | | | 4.3%[k] | 5%[k] | | | | |
| **All Discontinuations** | | 0%[a],1.8%[b], 7.1% on CsA, 12% on TAC[c] | | 3.1%[e] | 11.7%[k] 22.9%[m] | 10.1%[k], 12.2%[m] | 2%[o] | 6%[o] | 9%[o] | 12%[o] |
| **AE** | | | | | 2.5%[k] | 5.7%[k] | | | | |
| **GI** | | | | | 1.8%[k] | 1.9%[k] | | 2%[o] | 3%[o] | 3%[o] |
| **Diarrhea** | | | | | 1.2%[k] | 0.6%[k] | | | | |
| **All Interruption** | | 3% on CsA 2% on TAC[c] | | 1.9%[f] | | | | | | |
| **All Reduction** | | | | 6.3%[f] 4.9%[e] 10%91,[g] | | | 5%[n] | 2%[n] | | |
| **AE** | | | | 15%[h] | | | 12%[o] | 8%[o] | 11%[o] | 14%[o] |
| **GI** | | 1.8%[bd] | | 6%[g] | | | | | | |
| **Diarrhea** | | | | 4.2%[p] | | | | | | |
| **Hematological** | | | | 2%[g] | | | | | | |
| **Leukopenia** | | | | 1.7%[p] | | | | | | |
| **Anemia** | | | | 0.4%[p] | | | | | | |
| **Hyperbilirubinemia** | | | | 1.7%[p] | | | | | | |
| **Hyperuricemia** | | | | 0.4%[p] | | | | | | |

a= Abbud-Filho(2004)67 b=Nashan(2004)63 c=Tomlanovich(2006)[123] d=Nashan(2004)[64] e=Nashan(2006)[69] f=Pietruck(2005)[68] g=Massari(2005)[6] h=Massari(2004)[65] k=Budde(2004)[3] m=Budde(2006)[70] n=Budde(2005)[61] o=Budde(2006)[62] p=Duro Garcia(2004)[64]

## Tolerability: Conversion from MMF to MPS due to AEs

Converting a patient from MMF to MPS in an attempt to ameliorate side effects has been studied. Data reported by Chan[126] included a total of 328 patients (215 in cohort A and 113 in cohort B) that comprised the intent to treat population. At baseline, Cohort A had significantly higher scores on all GSRS subscales, and lower scores on GIQLI total and sub-scale scores compared to Cohort B (all P<0.0001). GIQLI total score was 90.4 $\pm$ 20.7 for Cohort A versus 122.7 $\pm$ 14.6 for Cohort B (P<0.0001) (Fig. 2). PGWBI total and subscale scores were also significantly lower for Cohort A versus Cohort B (all P<0.0001). At the second visit, 117 (66%) in cohort A reported an overall improvement in GI symptoms versus baseline while only eight patients (8%) in Cohort B reported an improvement. Physicians rated symptoms to be improving, remaining unchanged or worsening in 138 patients (78%), 33 patients (19%) and five patients (3%) in Cohort A, respectively, and in one (1%), 94 (93%) and six patients (6%) in Cohort B. The authors concluded that converting maintenance patients with mild to severe GI complaints from MMF to MPS significantly reduces the GI-related symptom burden and improves patient functioning and well-being within 4–6 weeks, as measured by patient-reported symptom and HRQoL questionnaires.

An analysis of renal transplants patients converted from MMF to MPS using patient-reported outcomes was recently published in an abstract on behalf of the PROGRIS Study Group.[127] Patients completed the following self-administered Gastrointestinal Quality of Life Index (GIQLI) and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires at baseline and 4-6 weeks after conversion. No protocol violations and/or premature discontinuation occurred in 177 of 215 patients (82%). Overall GSRS and GIQLI scores improved significantly between and visit 2. Age, MMF dose and choice of CNI did not influence benefit of conversion to MPS. Females seemed to benefit more. The authors concluded that conversion of MMF treated renal transplant patients with GI complaints to MPS may be beneficial.

An additional abstract describes the interim results of the *my*PROMS US02 Study Group.[123] Stable renal transplant recipients, at least 4 weeks post transplant with mild to moderate GI symptoms on MMF treatment, Cyclosporin (99 patients) or TAC (202 patients) with or without steroids were converted to an equimolar dose of MPS. Evaluations occurred at baseline, 1 month and 3 months. The average daily MPS dose as baseline and month 3 are reported in the table below.

| Average daily dose of MPS (mg/day) | CsA Group | TAC Group |
|---|---|---|
| Baseline | 1170 | 1070 |
| 3 month | 1180 | 1060 |

Dose interruptions were low at 3% for the CsA group and 2% for TAC. Dose reductions were 7.1% and 12.4% for CsA and TAC, respectively. AEs were reported at baseline and 3 months and are in the table below.

| | Baseline CsA | Baseline TAC | 3mo CsA | 3mo TAC |
|---|---|---|---|---|
| Diarrhea | 60.6% | 70.8% | 41.4% | 51.0% |
| GERD | 46.5% | 39.1% | 24.2% | 25.7% |
| Flatulence | 48.5% | 32.2% | 36.4% | 26.2% |
| Dyspepsia | 43.4% | 28.2% | 32.3% | 15.3% |
| Nausea | 43.4% | 27.7% | 24.2% | 19.8% |
| Abdominal distension | 38.4% | 27.2% | 24.2% | 17.8% |

Efficacy was measured as BPAR and few events were noted (CyA 2% versus TAC 1%). The authors concluded that conversion to MPS in combination with CyA or TAC is safe without compromising efficacy.

A second abstract from the same *my*PROMS US02 Study Group describes their finding in the subgroup of African Americans (AA).[128] A total of 101 patients (28 CyA, 73 TAC) were AA. AE baseline and 3 month data are in the table below.

| | Baseline CsA | Baseline TAC | 3mo CsA | 3mo TAC |
|---|---|---|---|---|
| Diarrhea | 60.7% | 69.9% | 39.3% | 53.4% |
| GERD | 53.6% | 42.5% | 28.6% | 26.0% |
| Flatulence | 60.7% | 39.7% | 39.3% | 27.4% |
| Dyspepsia | 28.6% | 27.4% | 17.9% | 12.3% |
| Nausea | 32.1% | 35.6% | 14.3% | 27.4% |
| Abdominal distension | 32.1% | 31.5% | 21.4% | 12.3% |

The GSRS questionnaire was completed and analysis of the scores demonstrated significant improvement in all scores after one month and thereafter. The authors concluded that conversion to MPS in patients with GI intolerance to MMF was beneficial.

Cantisani et al[97] describes a single-center study evaluating the use of MPS as a primary immunosuppressant or as a replacement for MMF in 90 liver transplant patients.[97] MPS was started at a median of 30 months post transplant. Mean age was 52.39 ± 11.08 years, 63% were men and then main indication for liver transplant was hepatitis C virus-induced cirrhosis. Mean administered daily dose was 720mg/day. Replacement of MMF occurred in 74.4%, while 12.2% were started on MPS due to loss of renal function, and 11.1% to treat an ACR. The results do not distinguish between those converting from MMF and those being initiated to mycophenolate.

Dumortier et al[90] described the conversion of liver transplant recipients from MMF to MPS due to GI AEs. Thirty-six treated with MMF since 18 months (3-28) and having GI disorders known for 9 months (3-12) were followed for 12 months (6-36). In the abstract the authors noted resolution in 55%, improved in 17% and unchanged or worse in 28%. In the manuscript it was noted that statistical analysis of each symptom disclosed that only diarrhea significantly decreased after conversion.[90]

## Precautions/Contraindications

### Precautions

A comparison of the precautions listed with MPS and MMF are detailed in the table below.

| | MPS | MMF |
|---|---|---|
| Gastrointestinal bleeding | + | + |
| Administer with caution in patients with active serious digestive disease | | + |
| Severe chronic renal impairment may result in higher plasma MPA and MPAG AUCs. No safety of long term exposure | + | + |
| Delayed graft function | + | + |
| Opportunistic infections in cardiac transplant patients | | Noted higher in CellCept treated patients vs. AZA |
| Herpes Simplex infections in cardiac transplant patients | | Noted higher in CellCept treated patients vs. AZA |
| Avoid concomitant administration with AZA due to bone marrow suppression and lack of clinical studies | | + |
| Concomitant administration of drugs that interfere with enterohepatic recirculation due to potential to reduce the efficacy (e.g. Cholestryamine) | + | + |
| Avoid use in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome | | + |
| Avoid use of live attenuated vaccines | + | + |
| Vaccinations may be less effective | + | |
| Risk of phenylketonuria | | + (oral suspension contains aspartame) |

### Warnings

Both agents (MMF and MPS) contain a warning in regards to the development of lymphomas and othe malignancies. Additionally both agents warn about use in pregnancy, use in combination with immunosuppressive agents other than antithymyocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, CsA and corticosteroids have not been determined and the development of neutropenia.

### Black Box Warnings

The current WARNING statement is present in the MPA PPI: Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use Myfortic® (mycophenolic acid). Patients receiving Myfortic should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.[12] A similar statement is found in the current MMFPPI.[129]

### Contraindications

Myfortic® is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil or to any of its excipients.[12]

## Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

**LA/SA for generic name Mycophenolate Sodium, Mycophenolate Acid:**

Potential name confusion: Mycophenolate Mofetil (CellCept): metformin (Fortamet): meloxicam (Mobic):; mefenamic acid (Ponstel): mepenzolate bromide (Cantil):

**LA/SA for trade name Myfortic®:**

Potential name confusion: Mobic®, Myproic®, Milophene®, Myadec®.: Mycobutin

## Drug Interactions

### Drug-Food Interactions

Compared to the fasting state, administration of EC-MPS with a high fat meal had no effect on MPA AUC; while there was a 33% decrease in $C_{max}$ and a significant delay in $T_{max}$.[9]

### Drug-Drug Interactions

Antacids: Absorption of a single dose of MPS was decreased when administered to 12 stable renal transplants patients taking magnesium-aluminum antacids. Both $C_{max}$ and $AUC_{(0-t)}$ were lower. It is recommended that data that antacids and MPS not be administered simulataneously.[12]

Cyclosporine: In stable renal transplant recipients CsA pharmacokinetics are unaltered by MPS.[12] In a randomized open-label, crossover trial chronic administration of cyclosporine with MPS sodium resulted in a 20-30% reduction in absolute bioavailability of MPA and a significant reduction in $AUC_{0-24}$.[50]

As MPS and MMF share the same active compound it is frequently predicted that drug interactions reported for MMF may also occur with MPS.[20] A review of general mechanisms for potential drug interactions finds concerns around interference with enterohepatic recycling, protein binding changes and competition between MPAG and other compounds for excretion at the renal tubule.[25] Since MPA is solely metabolized by glucuronidation, direct pharmacokinetic interactions with drugs metabolized by cytochrome P450 are not expected.

Acyclovir and Ganciclovir: Levels of acyclovir and ganciclovir (and MPAG) are increased if these agents are coadministered with MPS in patients with renal impairment.[15]

Bile-acid sequestrants: Due to the ability to reduce absorption and enterohepatic recirculation of MPA, there is concern around concurrent administration of MPS and bile-acid sequestrants.[2] Although no formal investigation exists it appears advisable to avoid use of cholestyramine and other drugs interfering with enterohepatic recirculation.[9]

Ferrous sulfate:[2] citing data by Morii et al describes a decrease in oral bioavailability of MMF when given concomitantly with ferrous sulfate.

Glucocorticoids: Glucocorticoids have been reported to induce glucoronosyltransferase expression, enhancing the activity of UDP-GT in rat hepatocyte cells in culture an in vivo in rodent animal models. Both UDP-GT 1a and 2B isoforms are up-regulated by dexamethasone in a dose- and time-related manner. Cattaneo et al[130] examined the effects of steroid withdrawal on MMF bioavailability in the same kidney transplant patients by comparing MPA PK at 6 months post-surgery (while on MMF and CsA), at the end of the steroid tapering phase (9 months post-transplant) and at follow-up (21 months post-transplant). The authors concluded that steroids affects MPA pharmacokinetics with discontinuation of steroid dose reducing the apparent plasma MPA clearance and enhancing the total bioavailability of the compound.

Sulfinpyrazone: A case of MMF toxicity has been reported in a female patient receiving sulfinpyrazone. It was postulated that there may have been interference with the renal tubular secretion of MPA leading to increased concentrations.[2]

Sirolimus: In a trial comparing sirolimus with CsA in combination with corticosteroids and MMF 2grams per day, MPA concentrations in the sirolimus group were higher.[121]

Tacrolimus: In a comparison trial of CsA plus MPS versus tacrolimus plus MPS, the administration of tacrolimus with MPS resulted in a ~20% increase in the total exposure of MPA with concomitant decreases in maximal concentrations and exposure to MPAG and acMPAG. As the study was powered to detect a >25% change the 20% increase was not statistically significant.

Concern has been expressed by many authors that alterations in protein binding / albumin binding with the coadministration of highly protein bound drugs (e.g. warfarin, aspirin) or changes in protein or albumin serum levels may result in an increase of free (unbound) MPA which may put patients at risk for MPA-related side effects.[9,20] One author noted the inclusion in the European package insert of a warning of increased MPA concentrations when MPS is given concomitantly with highly protein bound medications.[2]

Vaccinations: Concerns have been raised that vaccinations may be less effective and live vaccines should be avoided in patients receiving MPS.[9]

## Acquisition Costs

With each type of organ transplant a different dosage is utilized. The table below depicts equimolar dosages and their associated costs. Cost per unit is based on FSS pricing of March 27, 2007

| **CellCept®** | Daily | Monthly | Yearly |
|---|---|---|---|
| 1000 | $6.58 | $197 | $2364 |
| 1500 | $9.87 | $296 | $3552 |
| 2000 | $13.16 | $395 | $4740 |
| 2500 | $16.45 | $493 | $5916 |
| 3000 | $19.74 | $592 | $7104 |

| **Myfortic®** | Daily | Monthly | Yearly |
|---|---|---|---|
| 720 | $5.20 | $156 | $1872 |
| 1080 | $7.80 | $234 | $2808 |
| 1440 | $10.40 | $312 | $3744 |
| 1800 | $13.00 | $390 | $4680 |
| 2160 | $15.60 | $468 | $5616 |

## Treatment Population:

The number of patients with a history of transplantation along with their age was provided upon request by the VA National Transplant Program.[132] A total of 346 renal, 465 liver and 145 heart transplant recipients registered were believed living at the time of the requests. Some patients are noted to be recipients of other organs though data indicating the number of same organ transplants in the same patient were not requested or provided. The following provide the number of patients in each subset within the particular organ; the average, maximum and minimum age; as well as, the number and % of patients less than 75 and 65 years old. Many of the clinical trials have an age range at time of enrollment, often 18 – 75 or 18 – 65 years.

*Renal Transplant*

| Organ(s) | Kidney (cadaveric) | kidney (living) | Kidney (cadaveric) / Pancrease | Kidney (living) / Pancrease | Kidney / Pancrease | Kidney (cadaveric) / Liver | Combined |
|---|---|---|---|---|---|---|---|
| Number | 192 | 145 | 2 | 3 | 1 | 3 | 346 |
| Age | 58 | 53 | 51 | 47 | 51 | 52 | 55 |
| Max | 106 | 74 | 51 | 55 | | 58 | 106 |
| Min | 39 | 23 | 50 | 42 | | 47 | 23 |
| <75 years old | 189 | 145 | 2 | 3 | 1 | 3 | 343 |
| % of <75/total in column | 98.4% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 99.1% |
| <65 years old | 150 | 123 | 2 | 3 | 1 | 3 | 282 |
| % of <65/total in column | 78.1% | 84.8% | 100.0% | 100.0% | 100.0% | 100.0% | 81.5% |
| Time from Transplant | 886 | 1064 | 1608 | 1690 | 1687 | 218 | 968 |

*Liver Transplant*

| Organ(s) | Liver | Liver / Kidney | Liver / Kidney (cadaveric) | Combined |
|---|---|---|---|---|
| Number | 458 | 4 | 3 | 465 |
| Age | 53 | 52 | 54 | 53 |
| Max | 70 | 57 | 57 | 70 |
| Min | 24 | 47 | 50 | 24 |
| <75 years old | 457 | 4 | 2 | 339 |
| % of <75/total in column | 99.8% | 100.0% | 66.7% | 99.8% |
| <65 years old | 444 | 4 | 2 | 450 |
| % of <65/total in column | 96.9% | 100.0% | 66.7% | 96.8% |
| Time from Transplant | 999 | 592 | 635 | 994 |

*Heart Transplant*

| Organ(s) | Heart | Heart / Lung | Heart / Kidney | Combined |
|---|---|---|---|---|
| Number | 143 | 1 | 1 | 145 |
| Age | 52 | 53 | 60 | 54 |
| Max | 67 | | | 67 |
| Min | 21 | | | 21 |
| <75 years old | 143 | 1 | 1 | 145 |
| % of <75/total in column | 100.0% | 100.0% | 100.0% | 0.0% |
| <65 years old | 140 | 1 | 1 | 142 |
| % of <65/total in column | 97.9% | 100.0% | 100.0% | 97.9% |
| Time from Transplant | 1244 | 1068 | 728 | 1239 |

Upon review of the data provided a small discrepancy is noted between the renal and liver transplant downloads with the data from liver transplants noting 4 combination Liver and Kidney transplants who's donor (cadaveric or living) is not noted. The Complete Combined totals provided in the table below assume that these patients are not included in the renal transplant table.

| | |
|---|---|
| Number | 953 |
| Age | 54 |
| Max | 106 |
| Min | 21 |
| <75 years old | 949 |
| % of <75/total in column | 99.6% |
| <65 years old | 872 |
| % of <65/total in column | 91.5% |
| Average Time from Transplant | 1023 |

## Pharmacoeconomic Analysis

Published pharmacoeconomic evaluations of mycophenolate sodium were not located. Some published clinical studies indicate that higher than equimolar dosages of MPS may be attainable when patients are converted from MMF. While the

drug cost will increase with the higher dose, additional data indicates that the higher dose will result in a higher MPA AUC and a lower rate of BPAR and/or graft loss thus there is potential for costs savings. The majority of data indicates an equimolar dose or lower. Calculations below are based upon an equimolar dosage being achieved.

The lack of statistically significant differences in efficacy and safety parameters between MPS and MMF justify use of a cost minimization analysis.

| CellCept dose (mg) | Myfortic dose (mg) | Daily | 30day | Yearly |
|---|---|---|---|---|
| 1000 | 720 | $1.33 | $39.60 | $481.80 |
| 1500 | 1080 | $1.99 | $59.40 | $722.70 |
| 2000 | 1440 | $2.64 | $79.20 | $963.60 |
| 2500 | 1800 | $3.30 | $99.00 | $1,204.50 |
| 3000 | 2160 | $3.96 | $118.80 | $1,445.40 |

The table above indicates an annual savings of $481.80 to $1445.40 per patient per year when switching from MMF to MPS on an equimolar basis.

Utilizing the patient numbers provided by the VA Transplant Program described in the previous section and the typical daily dosage for each organ transplant type the following costs savings estimates can be derived:

| Organ \ Estimates | Low (Myfortic mg/day) | High (Myfortic mg/day) |
|---|---|---|
| Liver | $224,037 (720) | $336,055 (1080) |
| Renal | $250,054 (1080) | $333,405 (1440) |
| Heart | $174,653 (1520) | $209,583 (2160) |
| Estimated Annual Savings | $648,744 | $879,043 |

Conversion from MMF to MPS at current prices detailed in VA McKesson and NAC contracts will results in cost savings for each organ transplant type.

## Conclusions

Ideally, immunosuppressive agents should prolong patient and graft survival, reduce or prevent rejection episodes, target specific areas of the immune system to reduce the risk for infection or malignancy, exhibit predictable pharmacokinetics, and cause minimal toxicity.[18] Renal graft survival, using adjunct immunosuppressant regimens, is high, with rates of >88% for cadaveric grafts at 1 year post-transplantation, whereas >94% of grafts from living donors are surviving at 1 year post-transplant.[9]

Mycophenolate Sodium (MPS, Myfortic) was originally developed in an attempt to reduce the rate of gastrointestinal adverse events (GI AEs) experienced when mycophenolate mofetil (MMF, CellCept) was administered as part of an immunosuppressive regimen. The occurrence of GI AEs often leads to an interruption in medication administration, reduction in dose or discontinuation of the agent. Each of these events has an impact on treatment failure (e.g. BPAR, BPCR, graft failure or death) at a unique rate.

Two clinical trial series (ERL B301[4] and ERL B302[3]) comparing MPS to MMF in renal transplant recipients are often quoted as the pivotal trials that led to approval of MPS in the United States and Europe. ERL B301 was a 12 month trial that demonstrated the therapeutic equivalents of MPS to MMF in *de novo* first cadaveric or living-unrelated renal transplant patients. ERL B302 demonstrated 12 month safety and efficacy after conversion of patients from MMF to MPS in first or second cadaveric or living kidney transplant recipients. Both trials then entered an open-label phase with the patients in the MMF groups being converted to MPS. In ERL B301 the only AE reaching a statistical difference was the incidence of severe pneumonia ($P = 0.01$) while GI AEs were comparable. In ERL B302 only serious infections associated with MPS were significantly difference ($P =<0.05$). While the rates of all AEs and GI AEs are highly variable from study to study, a statistically significant difference in the rate of GI AEs between MPS and MMF has yet to be demonstrated. Data on the use of MPS in liver transplantation is now rising. Beyond abstracts, one retrospective and one prospective trial reporting on conversion from MMF to MPS are noted. Data on the use of MPS in heart transplantation is limited to one published trial with two preceding abstracts.

Pharmacokinetic (PK) studies, both single dose and maintenance trials, have demonstrated that MPS is able to achieve similar AUC and $T_{max}$. While some studies have noted a higher percentage of patients achieving a recommended >30mg*h/L when administered MPS a difference in clinical outcomes has not been statistically demonstrated. Due to the enteric coating MPS is unable to dissolve until the tablet has past the stomach. This has led to a consistently higher $C_{max}$ and in some cases led to the loss of a second peak of Mycophenolic Acid (MPA) that occurs when MMF is administered

and MPA experiences enterohepatic recirculation. The majority of PK trials have been performed on maintenance renal transplant patients. Newer data in liver transplant recipients indicates a similar pattern. Some recent abstracts have noted a high level of interpatient variability in measured MPA AUCs after MPS administration while patients receiving MMF are more consistent. While this may be an issue for therapeutic monitoring programs which has been advocated by many publications, an impact on clinical outcomes has not been demonstrated.

"The variable absorption for MMF and EC-MPS prohibits indiscriminate switching between EC-MPS and MMF, for example, on a daily basis."[9] In addition to the ERL B302 series many other studies, comparative and single-arm, have studied the studied conversion from MMF to MPS and demonstrated similar safety, tolerability and efficacy. In some trials the method dictated conversion on an equimolar basis while one series (*my*PROMS LA01) converted MMF patients to equimolar or higher doses with mixed success. Data on the conversion from MPS to MMF was not located. Other than suggesting the use of equimolar dosing if such an action is required, no other recommendations may be made based on the lack of evidence.

The time span of AE data is now 0-36 months in at least two study series with many other publications and series, including *my*PROMS, adding to the pool. Clinical and statistical differences have yet to be identified. Utilizing validated self-administered and practitioner-administered questionnaires, data has been published that illustrates a potential benefit in Health Related Quality of Life (HRQOL) from converting patients receiving MMF and experiencing GI AEs to MPS. It is also widely recognized that AEs may result in an interruption or reduction in MPS or MMF dose. In comparative studies the rates of interruption or reduction have failed to reach a statistical difference. Single arm studies provide similar results though there is wide intervariability.

Reports and data on drug interactions involving MPS are few with the majority of warnings derived from data on MMF. It is widely believed that MPS and MMF share equivalent risks of drug interactions as they both results in MPA levels.

Caution must be exercised in evaluating published trials on MPS. Many of the studies are sponsored by the pharmaceutical manufacturer though not all articles clearly identify this. Few of the authors offer any disclosure. All 3 study series noted in the document (ERL B301, ERL B302 and *my*PROMS) are manufacturer sponsored trials. Many abstracts are included in this document even though published data is available as discrepancies and omissions are noted.

Given the presence of equimolar dosages and a growing amount of data that demonstrates therapeutic equivalence and similar safety profile, the agent with the lowest expense is likely to provide the same clinical benefit. The cost of implementation should be evaluated thoroughly before a therapeutic conversion from MMF to MPS occurs. This should include assessment for precautionary clinic visits and / or laboratory monitoring of serum MPA levels. While the difference in the incidence of therapeutic failure, BPAR, BPCR, graft loss or, most significantly, death is low in most conversion studies comparing MMF and MPS, any one of these events could still lead to a significant decrease in cost savings realized.

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## Appendix: Clinical Trials

The initial literature search was performed on OVID (1966 to January 2006 including publications in progress) on January 6, 2006 using the search terms "mycophenolate sodium.mp. [mp=ti, ot, ab, nm, hw]". A manufacturer's AMCP dossier was not available though personal communication indicated one was being developed. Where it was determined to be relevant review articles were incorporated. The search was limited to studies published in English language.

An updated literature search using the same term was performed on OVID on September 15, 2006.

An updated literature search was performed on PubMed/Medline using the same term was performed on December 15, 2006.

A clinical trial summary is presented for clinical trials included in this document. They are sorted in alphabetical order of the primary author with a secondary sort of chronology when multiple articles have been presented by the primary author. Abstracts have been excluded but citations are listed in the reference section.

Appendix: PK Studies

PK Study Characteristics

| Author | Abstract | Year | Total #patient | Patient Population | Design | AUC time frame (h) | MMF Dose (mg) | Administration freq | Duration | Steroid |
|---|---|---|---|---|---|---|---|---|---|---|
| Schmouder[37] | Y | 1999 | 24 | stable renal transplants | Crossover | 0-48 | 1000 | single dose | | |
| Grainger[14] | N | 2001 | 48 | *de novo* | | ? | 1000 | BID? | 14,90, 180d | Y |
| Schmouder[38,39] | Y | 2002 | 51 | part of phase III *de novo* | | 0-12 | 1000 | BID | 14,90,180d | Y |
| Budde[40] | Y | 2002 | 14 | RT that had been maintained on MMF | Double-blind, double-dummy, 5 PK profiles | 0-11 | 1000 | BID | 15mo | |
| Gabardi[2] citing Schmouder (2002)[38] Abstract data | | 2003 | 51 | | randomized, double-blind, double -dummy | 0-24 | 1000 | BID | 180d | |
| Arns[28] | Y | 2004 | 16 | stable renal transplants | Crossover | ? | | single dose | | |
| Arns[28] | Y | 2004 | 16 | stable renal transplants | Crossover | ? | | single dose | | |
| Arns[28] | Y | 2004 | 16 | stable renal transplants | Crossover | ? | | single dose | | |
| Arns[28] | Y | 2004 | 16 | stable renal transplants | Crossover | ? | | single dose | | |
| Budde[41] | Y | 2004 | 16 | Maintenance renal transplants | Crossover, open-label | 0-12 | ? | ? | 14d | |
| Tedesco-Silva[42,43] | Y | 2004 | 40 | stable for >30days | | 0-12 | | ? | 30d | |
| Sumethkul[113] | Y | 2004 | 12 | First dose | | 0-12 | | | PK at initial dose and 2wks, outcome followed for 3-8mo | Y |
| Arns[7] | N | 2005 | 24 | >3mo post 1st or 2nd RT | Crossover, 3 way, randomized | 0-48 | 1000 | single dose | | |
| Arns[7] | N | 2005 | 24 | >3mo post 1st or 2nd RT | Crossover | 0-48 | | single dose | | |
| Sumethkul[35] | N | 2005 | 12 | *de novo* | | 0-12 | | BID | PK at initial dose and 2wks, outcome followed for 3-8mo | Y |
| Kaplan[110] | N | 2005 | 12 | 1st or 2nd transplant >9mo, stable for >6mo | Crossover of Cyclosporine | 0-12 | | BID | 14d | Y |
| Kaplan[110] | N | 2005 | 12 | 1st or 2nd transplant >9mo, stable for >6mo | Crossover of Tacrolimus | 0-12 | | BID | 14d | Y |
| Tedesco-Silva[30] | N | 2005 | 40 | stable for >30days | Open-label, crossover | 0-12 | 1000 | BID | 28d | ? |
| He[44] | Y | 2006 | 24 | Subset of ERL B302 population | Double-blind, double-dummy, randomized | | | | Day 1, 3 months, 12months | |
| Merlini[45] | Y | 2006 | 20 | Stable renal transplant | ? | | | | 6, 12 months post-transplant | |
| Perry[8] | Y | 2006 | 13 | Liver Transplants >12mo | Single arm, interim analysis | 0-12 | | Single dose | | |
| Stracke[36] | Y | 2006 | 17 | Renal transplant <3 weeks post tx | | 0-12 | | | | |
| Arns[133] | Y | 2006 | 21 | Tacrolimus patients converted from MMF to MPS | | | | | | |

# PK studies: MMF data

| Reference | MMF patients | MMF: MPA Cmax (mcg/mL) | MMF: MPA Tmax (h) | MMF MPA AUC (mcg*h/mL) | MMF: MPA Cmin (mcg/mL) | MMF: MPAG Cmax (mcg/mL) | MMF: MPAG Tmax (h) | MMF MPAG AUC (mcg*h/mL) | MMF: acMPAG Cmax (mcg/mL0 | MMF: acMPAG Tmax (h) | MMF acMPAG AUC (mcg*h/mL) | MPS: #patient | MPS Dose (mg) | MPS: MPA Cmax (mcg/ml) | MPS: MPA Tmax (h) | MPS: MPA AUC (mcg*h/ml) | MPS: MPA Cmin (mcg/ml) | MPS: MPAG Cmax (mcg/mL) | MPS: MPAG Tmax (h) | MPS MPAG AUC (mcg*h/mL) | MPS: acMPAG Cmax (mcg/mL) | MPS: acMPAG Tmax (h) | MPS acMPAG AUC (mcg*h/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schmouder[37] | 24 | 30.2 | 0.8 | 60.8 | | 60.8 | 2 | 1167 | | | | 24 | 720 | 26.1 | 2 | 62.1 | | 62.4 | 2.5 | 1076 | | | |
| Grainger[14] | 28 | 11.6, 17.9, 18.6 | | 23.3, 39.1, 37.2 | | | | | | | | 27 | 720 | 13.9, 24.6, 23 | | 29.1, 50.7, 55.7 | | | | | | | |
| Schmouder[38,39] | 27 | | | 23.2, 39.1, 37.2 | | | | | | | | 24 | 720 | | | 29.1,50.7, 55.7 | | | | | | | |
| Budde[40] | ? | 20.2±8.9 | 0.9 ±0.4 | 55.7 ±9.9 | | | | | | | | ? | 720 | 19.2±8.9 | 2.3±1.4 | 56.0±15.3 | | | | | | | |
| 2 | 27 | 18.6 | | 37.2 | | | | | | | | 24 | 720 | 23 | | 55.7 | | | | | | | |
| Arns[83] | | | | | | | | | | | | 16 | 720 | 16.7 | | 42.4 | | | | | | | |
| Arns[83] | | | | | | | | | | | | 16 | 180 | 5.3 | | 8.9 | | | | | | | |
| Arns[83] | | | | | | | | | | | | 16 | 360 | 9 | | 20.2 | | | | | | | |
| Arns[83] | | | | | | | | | | | | 16 | 2160 | 40.1 | | 121 | | | | | | | |
| Budde[41] | 16 | 15.37 ±8.2 | | 33.5 ±9.6 | | | | 551.1±377 | | | | 16 | ? | 13.57±6.4 | | 36.40±15.9 | | | | 652±407 | | | |
| Tedesco-Silva[42,43] | | | | | | | | | | | | 40 | stable | 33.4 | 2.5 | 74.7 | | 223.7 | 4 | 1723.7 | 4.1 | 3 | 19.6 |
| Sumethkul[113] | | | | | | | | | | | | 12 | 720 | | | 73.9±49.5 (31.9-190) | | | | 406±133 (243-646) | | | |
| Arns7 | 24 | 30.2 | | 63.7 | | | | | | | | 24 | 640 | 30.1 | | 60.7 | | | | | | | |
| Arns7 | | | | | | | | | | | | 24 | 720 | 26.1 | | 66.5 | | | | | | | |
| Sumethkul[35] | | | | | | | | | | | | 12 | 720 | | | 73.9±49.5 (31.9-190) | | | | 407±134 (243-646) | | | |
| Kaplan[110] | | | | | | | | | | | | 12 | 720 | 23.66 ±9.68 | 2.54 | 47.6±15.9 | | 128.93 ±32.57 | 3.98 | 1104.57 ±394.73 | 3.36 ±1.25 | 2.79 | 13.20 ±5.11 |
| Kaplan[110] | | | | | | | | | | | | 12 | 720 | 19.04 ±8.58 | 3.02 | 58.8±25.2 | | 95.99 ±21.25 | 2.77 | 760.59 ±189.23 | 2.16 ±0.89 | 3.27 | 8.82±3.90 |
| Tedesco-Silva[30] | 40 | 25.5 | 1.0 | 61.4 | | 184.7 | 2.5 | 1412.8 | 3.9 | 1 | 18.8 | 40 | 720 | 33.4 | 2.5 | 74.7 | | 223.7 | 4 | 1723.7 | 4.1 | 3 | 19.6 |
| He[44] | 11 | 25.8 | | 59.0 | | | | | | | | 13 | | 22.3 | | 64.5 | | | | | | | |
| Merlini[45] | 10 | | | | 1.3 ± 0.8 | | | | | | | 10 | | | | | 5.9 ± 5.01 | | | | | | |
| Perry[8] | | | | | | | | | | | | 13 | 720 | TAC: 30.6 ± 21.7, CsA: 21.9 ± 10.9, p=0.24 | TAC: 30.6 ± 21.7, CsA: 21.9 ± 10.9, p=0.24 | TAC 59.0 ± 35.9; CsA 41.0 ± 28.1, p=0.24 | | | | | | | |
| Stracke[36] | | | | | | | | | | | | 17 | 720 | 7.02 (2.75-16.7) | 7.02 (2.75-16.7) | 26.0 (15.9-40.9) | | 212 (159-295) | 4.0 (0.1-6.0) | 1987 (1498-3250) | | | |
| Arns[133] | 21 | | | 39.3 | | | | | | | | 21 | | | | 43.2 | | | | | | | |