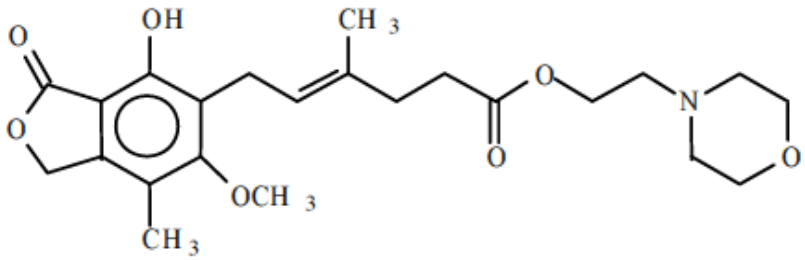
APO-MYCOPHENOLATE CAPSULES

NAME OF THE MEDICINE

Mycophenolate mofetil

Chemical Name: 2-morpholinoethyl(E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl4-hexenoate

Structural Formula:



Molecular Formula: $C_{23}H_{31}NO_7$

Molecular Weight: 433.50

CAS Registry Number: 115007-34-6

DESCRIPTION

Mycophenolate mofetil (MMF) is a white to off-white crystalline powder. It is freely soluble in dimethyl sulfoxide, tetrahydrofuran, acetone, acetonitrile, dichloromethane, and ethyl acetate; soluble in methanol and propylene carbonate; sparingly soluble in anhydrous ethanol; slightly soluble in 2-propanol, diethyl ether, and very slightly soluble in hexane. It is practically insoluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6).

Each capsule contains 250mg Mycophenolate Mofetil as the active ingredient.
In addition each capsule contains the following inactive ingredients:
Capsule fill: Croscarmellose sodium, Magnesium stearate
Capsule shell: Gelatine, Indigo carmine, Iron oxide red, Titanium dioxide, water - purified, Sodium lauryl sulfate, black printing ink (TEK SW 9008).
Black printing ink (TEK SW 9008) – Shellac, Dehydrated alcohol, Isopropyl alcohol, Butyl alcohol, Propylene glycol, Strong ammonia solution, Black iron oxide, Potassium hydroxide, Water - purified.

PHARMACOLOGY

Mechanism of Action

Mycophenolic acid (MPA) is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) which inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Based on Chinese hamster inosine-5 ’-monophosphate dehydrongenase (IMPDH) in complex with inosine5’-monophosphate (IMP) and mycophenolic acid (MPA), the mechanism by which MPA inhibits the enzymic activity of IMPDH (human type II) appears to be related to the ability of MPA to structurally mimic both the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthos-5 ’- monophosphate, the committed step in the de novo guanosine nucleotide biosynthesis. Human type II and Chinese hamster IMPDH differ by six amino acids but have similar enzymatic characteristics. MPA has more potent cytostatic effects on lymphocytes than on other cells because T- and B-lymphocytes are dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilise salvage pathways. Depletion of guanosine nucleotides leads to the inhibition of glycosylation of adhesion molecules on

lymphocytes, a process also considered an action of mycophenolate mofetil.
Mycophenolate mofetil (MMF) has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). MMF has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. MMF was used alone or in combination with other immunosuppressive agents in these studies.

In experimental animals, MMF has been demonstrated to prevent inflammatory responses that are immunologically mediated, and to delay tumour development and prolong survival in models of xenogeneic human to mouse and syngeneic murine tumours in vivo.

MMF, the 2-morpholinoethyl ester of MPA is rapidly absorbed following oral administration and hydrolysed to form free MPA, which is the active metabolite. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation.

Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes, showing the specificity of action of the drug. MPA also suppresses antibody formation by B-lymphocytes. By depletion of guanosine nucleotides, MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells. By this mechanism, MPA may inhibit recruitment of leucocytes into sites of inflammation and graft rejection.

MMF did not inhibit early events in the activation of human peripheral blood mononuclear cells such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Animal studies have shown that mortality in rats with Pneumocystis carinii pneumonia is higher during combined treatment with MMF and trimethoprim/sulfamethoxazole than with either drug alone. MMF did not interfere with the ability of trimethoprim/sulfamethoxazole to reduce the incidence of P. carinii cysts in surviving animals, and reduced the incidence of cysts when administered by itself.

Pharmacokinetics
Absorption
Following oral and intravenous administration, MMF undergoes rapid and extensive absorption and complete pre systemic metabolism to the active metabolite, mycophenolic acid (MPA). MMF is not measurable systemically in plasma following oral administration. Modest concentrations of the parent drug are detected in plasma samples during intravenous infusion, but concentrations decline rapidly after the completion of the infusion. The mean extent of absorption of MPA during multiple dosing (as measured by the area under the plasma-concentration time curve, AUC) increases in a dose proportionate manner over a daily dose range of 1 g to 4 g in renal transplant patients.

The administration of a 1.5 g dose of MMF by the intravenous and oral routes to healthy volunteers resulted in similar plasma MPA and inactive glucuronide of MPA (MPAG) total AUC values. Recovery of MPAG in urine was the same for both routes indicating complete absorption of oral MMF. The mean bioavailability of orally administered MMF, based on MPA AUC, was 94% relative to IV administration.

In a steady state study, the administration of 1 g twice daily (bd) of MMF by the IV and oral routes to renal transplant patients in the immediate post-transplant period, resulted in a MPA AUC that was approximately 29% higher for the IV formulation than achieved by the capsule. C_{max} was approximately 20% greater for IV.

The results of a single-dose bioequivalence study in 47 healthy volunteers indicated that the 500 mg tablet (x 2) was equivalent to the 250 mg capsule (x 4) with respect to the extent of absorption (AUC), but not the rate of absorption (C_{max}). The C_{max} for MPA of the tablet was 28% lower than that for the capsule.

In a two-way, randomised cross-over, bioequivalence study of MMF oral suspension and capsules, a 1 g dose of MMF suspension was bioequivalent to the 250 mg capsule (x 4) with respect to C_{max}, $t_{1/2}$, AUC_{last}, $AUC_{0-\infty}$ and K_{el}, T_{max} was marginally shorter for the oral suspension.

Food had no effect on the extent of absorption (MPA AUC) of MMF when administered as 1.5 g bd doses to renal transplant patients. However, the C_{max} for MPA was decreased by 40% in the presence of food.

The pharmacokinetic profile of MPA in cardiac patients is similar to that in renal patients.

Distribution
As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed approximately 6 to 12 hours post-dose. Co-administration of cholestyramine (4 g tid) with MMF is associated with a reduction in the AUC of MPA of approximately 40% as a result of decreased enterohepatic recirculation. The majority of the difference in the AUC is in the terminal portion of the MPA plasma concentration time profile.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

Metabolism
MPA is metabolised principally by glucuronyl transferases to form the pharmacologically inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is converted to free MPA via enterohepatic recirculation.

Elimination
After oral administration, 93% of the dose was recovered from the urine and 6% from the faeces. The major metabolite of MMF excreted in urine is MPAG, which accounts for 87% of the oral MMF dose. Less than 1% of the dose was excreted as MPA in the urine. The following metabolites of the morpholino moiety are also recovered in the urine following oral administration of MMF: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N- oxide of N-(2-hydroxyethyl)-morpholine.

Mean ± SD apparent half-life and plasma clearance of MPA are 17.9 ± 6.5 hours and 193 ± 48 mL/min respectively following oral administration and 16.6 ± 5.8 hours and 177 ± 31 mL/min respectively following intravenous administration.

Pharmacokinetics in Special Populations
Renal, Cardiac and Hepatic Transplant Patients: In renal, cardiac and hepatic transplant patients, mean steady state MPA AUC and C_{max} were up to 40% lower in the early post-transplant period (< 40 days post-transplant) compared to the late transplant period (3 - 6 months post-transplant).

In renal transplant patients, in the immediate post-transplant phase, mean steady state MPA AUC was 24% higher following 1 g bd intravenous MMF (over 2 hours) for 5 days compared with the same dose orally.

In cardiac transplant patients, administration of 1.5 g bd oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered the same dose.

In hepatic transplant patients, administration of 1 g bd intravenous MMF followed by 1.5 g bd oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered 1 g bd oral MMF.

Renal Impairment: In a single dose study (6 subjects per group), plasma MPA AUCs were up to 30% higher in subjects with mild to moderate renal impairment (GFR 25 - 80 mL/min/1 .73m2) and 75% higher in subjects with severe renal impairment (GFR < 25 mL/min/1 .73m2) than those subjects with normal renal function (GFR > 80 mL/min/1 .73m2). The mean increase in MPA AUC observed in subjects with severe renal impairment was comparable to the increase in MPA AUC seen when the dose of MMF is increased from a daily dose of 2 to 3 g (Refer to DOSAGE AND ADMINISTRATION). Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied. In addition, the single dose plasma AUC of MPAG was 3 to 6 fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Delayed Renal Graft Function Post-Transplant: In patients with delayed renal graft function post-transplant, mean AUC_{0-12} of MPA was comparable to that seen in post-transplant patients without delayed graft function. However, mean plasma AUC_{0-12} of MPAG was 2- to 3-fold higher than post-transplant patients without delayed graft function. Also, with repeated dosing, plasma concentrations of MPAG accumulated, whereas accumulation of MPA occurred to a lesser degree, if at all. High plasma concentrations of MPAG may displace MPA from its protein binding sites resulting in a transient increase in the plasma concentration of free MPA in patients with delayed graft function.

No dose adjustment is recommended although close monitoring is advised.

Haemodialysis: The pharmacokinetics of MMF during haemodialysis are not altered. Haemodialysis does not remove MPA or MPAG. At high concentrations (> 100 µg/mL), haemodialysis removes only small amounts of MPAG.

Hepatic Impairment: In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation was relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Elderly Patients: Pharmacokinetics in the elderly have not been formally evaluated.

Paediatric Patients: The pharmacokinetic parameters of the MPA and MPAG were evaluated in 55 paediatric renal transplant patients aged 1 to 18 years given 600 mg/m2 MMF orally twice daily (up to a maximum of 1 g bd). This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g bd in the early and late post-transplant period. MPA AUC levels across age groups were similar in the early post- transplant period out to 9 months post-transplant. There is limited pharmacokinetic data available for children aged less than 2 years.

Plasma-Binding
MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges such as those normally seen in stable renal transplant patients; however at higher concentrations of MPAG which are seen in patients with delayed graft function or with severe renal insufficiency, the bound fraction in vitro decreases to 62%.

In vitro studies to evaluate the effect of several agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 250 µg/mL with HSA) and MPAG (at greater than or equal to 460 µg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, naproxen, digoxin, cyclosporin, theophylline, tacrolimus, tolbutamide, propranolol, warfarin, and prednisone did not increase the free fraction of MPA. MPA at concentrations as high as 100 µg/mL had little effect on the binding of warfarin, digoxin or propranolol but decreased the binding of theophylline from 53% to 45% and decreased the binding of phenytoin from 90% to 87%.

CLINICAL STUDIES

1. Prevention of Acute Renal Rejection Episodes
The safety and efficacy of mycophenolate mofetil as adjunctive therapy for the prevention of organ rejection following allogeneic renal transplants were assessed in three randomised, double-blind, multicentre trials.

These studies compared two dose levels of mycophenolate mofetil (1 g bd and 1.5 g bd) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporin and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced biopsy-proven acute rejection or treatment failure (defined as early termination from the study for any reason without prior biopsy- proven rejection) within the first six months after transplantation. Mycophenolate mofetil, when administered with ATGAM® induction (one study) and with cyclosporin and corticosteroids (all three studies) was shown to be superior to the following three therapeutic regimens: (1) ATGAM® induction / azathioprine / cyclosporin / corticosteroids, (2) azathioprine / cyclosporin / corticosteroids, and (3) cyclosporin / corticosteroids. The superior efficacy of mycophenolate mofetil as adjunctive therapy, when compared to azathioprine or placebo, was demonstrated by a reduction in the incidence of first biopsy-proven acute rejection episode or treatment failure within the first 6 months following transplantation. In addition, mycophenolate mofetil reduced the incidence of first biopsy-proven acute rejection episodes within the first six months after transplantation.

In the table below, the percentages for first biopsy-proven rejection alone have not been adjusted for

patients who terminated prematurely before experiencing a biopsy-proven rejection episode.

Incidence of Biopsy Proven-Rejection or Treatment Failure

Induction, Azathioprine-Controlled (n=499)	**Azathioprine 1-2 mg/kg/day (n = 166)**	**MMF 2 g/day (n = 167)**	**MMF 3 g/day (n = 166)**
First biopsy - proven rejection episode or treatment failure	47.6%	31.1%	31.3%
First biopsy - proven rejection episode alone	38.0%	19.8%	17.5%
No Induction, Azathioprine Controlled (n = 503)	**Azathioprine 100-150 mg/day (n = 166)**	**MMF 2 g/day (n = 173)**	**MMF 3 g/day (n = 164)**
First biopsy – proven rejection episode or treatment failure	50.0%	38.2%	34.8%
First biopsy – proven rejection episode alone	35.5%	19.7%	15.9%
No Induction, Placebo-Controlled (n=491)	**Placebo (n = 166)**	**MMF 2 g/day (n = 167)**	**MMF 3 g/day (n = 166)**
First biopsy – prove rejection episode or treatment failure	56.0%	30.3%	38.8%
First biopsy – proven rejection episode alone	46.4%	17.0%	13.8%

Incidence of Biopsy Proven-Rejection or Treatment Failure
In these three studies, the proportion of patients requiring antilymphocyte therapy for treatment of rejection during the first 6 months following transplantation was smaller among patients receiving mycophenolate mofetil 2 g per day (5.5 to 10.3%) or mycophenolate mofetil 3 g per day (3.1 to 5.4%) than among patients receiving azathioprine or placebo (15 to 21%).

Six and twelve month patient survival and graft survival was somewhat higher in the patients receiving mycophenolate mofetil in comparison to either azathioprine or placebo. The cumulative proportions of patients who had died or lost their graft by 6 and 12 months post-transplant were as follows:

Cumulative Incidence of Combined Graft Loss & Patient Death at 6 (12) Months

Study	**Control (Azathioprine or Placebo)**	**MMF 2 g/day**	**MMF 3 g/day**
Induction, Azathioprine-Controlled	10.4% (12.2%)	5.5% (8.5%)	8.5% (11.5%)
No Induction, Azathioprine-Controlled	11.7% (13.6%)	8.8% (11.7%)	6.7% (11.0%)

No Induction, Placebo-Controlled	10.2% (11.5%)	6.7% (8.5%)	8.8% (10.0%)

2. Treatment of Refractory Renal Rejection

The safety and efficacy of mycophenolate mofetil as adjunctive therapy for the treatment of refractory organ rejection following allogeneic renal transplants was assessed in one randomised, open-label, multicentre trial. This study was designed to evaluate whether mycophenolate mofetil at a dose of 1.5 g bd was superior to high dose IV steroids. In this study, all patients continued to receive concomitant maintenance oral corticosteroids and cyclosporin. The control group received IV methylprednisolone (5 mg/kg/day for 5 days followed by an oral course with tapered doses of corticosteroids); the control patients also generally received azathioprine. A total of 150 patients were enrolled (73 assigned to receive IV steroids; 77 assigned to receive mycophenolate mofetil). Patients enrolled in this study had recurrent or persistent allograft rejection following treatment with either Orthoclone OKT3®, ATGAM®, or antilymphocyte globulin for at least 7 days, the last day of which occurred within 28 days prior to entry into the study. In addition, patients showed renal biopsy findings consistent with acute rejection at study entry. Serum creatinine concentrations were 442 µmol/L or lower at study entry.

The primary efficacy endpoint was graft and patient survival at 6 months post-enrolment. Mycophenolate mofetil was shown to be clinically effective in this study as evidenced by a 45% reduction in the number of patients who died or lost their graft. By 6 months post-enrolment, 26% of the IV steroid group and 14.3% of the mycophenolate mofetil group had died or experienced graft loss. Eighteen patients (25%) receiving high dose IV steroids and 9 patients (12%) receiving mycophenolate mofetil lost their graft in the 6 months after enrolment. One patient (1.4%) receiving high dose IV steroids and 2 patients (2.6%) receiving mycophenolate mofetil died in the 6 months after enrolment. Fewer patients receiving mycophenolate mofetil (10.4%) required treatment with anti-lymphocyte preparations in the 6 months after enrolment, compared to those receiving high dose IV steroids (24.7%).

3. Prevention of Renal rejection in Paediatrics

In a multicentre open-label, safety, tolerability and pharmacokinetic study of MMF oral suspension 600 mg/m2 bd (up to 1 g bd) in combination with cyclosporin and corticosteroids in the US, Europe and Australia, 100 patients aged 3 months to 18 years of age received treatment for the prevention of renal allograft rejection. The primary efficacy endpoint was the proportion of patients experiencing an acute rejection episode in the first 6 months post-transplant. Results were analysed after 1 year and it was shown that MMF was well tolerated in paediatric patients (see ADVERSE EFFECTS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bd MMF capsules (see **PHARMACOLOGY: Pharmacokinetics: Special Populations).** The rate of biopsy-proven rejection was similar across the age groups (3 months to < 6 years, 6 to < 12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant were similar to the rates observed in adult renal transplant patients. Results out to 36 months post-transplant in children are currently under investigation.

4. Prevention of Cardiac Allograft Rejection

In a randomised, double-blind, parallel active-controlled multicentre study to compare the safety and efficacy of MMF 1.5 g bd with azathioprine 1.5 - 3 mg/kg/day, both in combination with cyclosporin and corticosteroids, 650 patients were randomised to the two arms. The primary endpoints investigated were (1) prevention of biopsy-proven acute rejection with haemodynamic compromise during the first six months following transplantation and (2) prevention of death or retransplantation during the first year following cardiac transplantation. 72 patients were withdrawn prior to administration and without knowledge of the assigned therapy primarily because of perioperative adverse events, inability to take oral medication or death. Therefore, 289 patients received study medication in each arm.

Patients in the mycophenolate mofetil arm had a lower incidence of death or retransplantation, however this difference was within the protocol-defined range of equivalence, being a ± 10% mortality difference.

Mycophenolate mofetil and azathioprine did not differ significantly at 6 months in biopsy-proven acute rejection with haemodynamic compromise. Survival, acute rejection and composite endpoints are listed in the table below.

Parameter	Azathioprine n = 289	MMF n = 289
Survival Endpoint		
Death or retransplantation at 12 months post-transplant	11%	6%
Composite Failures at 12 months		
Death, ejection fraction < 30%, coronary stenosis or myocardial infarction	14%	8%
Acute Rejection Endpoints		
Patients with Rejection at 6 months post-transplant		
1. Including haemodynamic compromise (1)		
- with haemodynamic compromise	35%	32%
- with severe haemodynamic compromise (cardiogenic) (2), (3)	17%	11%
2. By ISHLT Grade		
- grade 1A or greater	97%	95%
- grade 2A or greater	69%	65%
- grade 3A or greater	53%	45%
3. Including pulse treatment of rejection		
- biopsy proven rejection		
treated with pulse immunosuppressives (4)	71%	64%
- biopsy proven or presumed rejection		
treated with pulse immunosuppressives (4)	74%	66%
treated with OKT3 or ATG	21%	15%

(1) Haemodynamic compromise defined as one or more of the following:
Pulmonary capillary wedge pressure ≥ 20 mm or 25% increase
Cardiac index < 2.0 or 25% decrease
Ejection fraction ≤ 30%
Pulmonary artery saturation ≤ 60% or 25% decrease
Presence of S3 gallop
Fractional shortening ≤ 20 % or 25% decrease

(2) Severe defined as requirement for inotropic support to manage any one of the clinical conditions listed above.

(3) Amongst patients who reached this acute rejection endpoint, no mycophenolate mofetil-treated patients died during 12 months, versus 8 AZA recipients during 6 months and 12 AZA recipients who died during 12 months.

(4) Pulse immunosuppressives being corticosteroids and if required OKT3 by protocol-defined regimen (according to the International Society for Heart and Lung Transplantation (ISHLT) biopsy grade and degree of haemodynamic compromise).

5. Prevention of Hepatic Allograft Rejection

The safety and efficacy of mycophenolate mofetil was assessed in a randomised, double-blind, parallel, active-controlled, multicentre study in hepatic transplant patients. This study compared the use of mycophenolate mofetil 1 g bd intravenously for up to 14 days followed by 1.5 g bd orally against azathioprine 1 – 2 mg/kg/day intravenously followed by 1 – 2 mg/kg/day orally, both in combination with cyclosporin and corticosteroids. 565 patients were randomised into the two arms, 278 patients in the mycophenolate mofetil group and 287 patients in the azathioprine group.

The two primary endpoints investigated were (1) the proportion of patients who experienced, in the first 6 months post-transplantation, (a) one or more episodes of biopsy-proven and treated rejection or (b) death/retransplantation, and (2) the proportion of patients with graft loss (death/retransplantation) during the first 12 months post- transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/retransplantation) for 1 year.

In the primary analyses mycophenolate mofetil in combination with corticosteroids and cyclosporin was superior to azathioprine for prevention of acute rejection ($p = 0.02$) in the 6 months following transplant and equivalent to azathioprine for survival or graft loss in the 12 months following transplant.

	Azathioprine n =287	Azathioprine n =287	Difference [95% CI]
Biopsy - proven and treated rejection or death / retransplantation at 6 months	47.7%	38.1%	p=0.02
Death or retransplantation at 12 months	14.6%	14.0%	0.5(1) [-5.1,6.0]

(1) Weighted point estimate of difference in proportions (azathioprine minus MMF). Met non inferiority criterion of a lower bound > - 10%.

The superiority of mycophenolate mofetil to azathioprine in the time to biopsy-proven and treated rejection or death/ retransplantation in the 6 months following transplant approached statistical significance (log-rank p = 0.06). The time to death/retransplantation in the 12 months following transplant was similar in the two treatment groups (log-rank p = 0.86).

INDICATIONS

Mycophenolate mofetil is indicated for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants.

Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in paediatric patients (2 to 18 years) receiving allogeneic renal transplants.

CONTRAINDICATIONS

Allergic reactions to mycophenolate mofetil have been observed, therefore, mycophenolate mofetil is contraindicated in patients with a hypersensitivity to MMF or to mycophenolic acid.

Mycophenolate mofetil is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see **Use in Pregnancy**).

Mycophenolate mofetil is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see **Use in Pregnancy**).

Mycophenolate mofetil is contraindicated in women who are breastfeeding (see **Use in Lactation**).

PRECAUTIONS

General
Female patients of childbearing potential must use effective contraception before, during and for six weeks after receiving mycophenolate mofetil. Mycophenolate mofetil is contraindicated during pregnancy and during breastfeeding (see **Use in Pregnancy and Use in Lactation**).

Neoplasms
As with other patients receiving immunosuppressive regimes involving combinations of medicines, patients receiving mycophenolate mofetil as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than the use of any specific agent. Approximately 1% of patients receiving mycophenolate mofetil with other immunosuppressive agents in the controlled studies of prevention of rejection have developed lymphoproliferative disease or lymphoma. As immunosuppression increases the risk of skin cancer, patients should also be advised to limit their exposure to sunlight and other sources of UV light by wearing protective clothing and using sunscreen with a high protection factor.

Infections
Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis. In the controlled studies for the prevention of rejection, the incidence of fatal infection was similar in patients receiving mycophenolate mofetil or control therapy in combination with other immunosuppresive agents. There was a higher incidence of fatal

infection in the liver transplant study (5%) compared with the other studies (2%).

Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of progressive multifocal leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in mycophenolate mofetil-treated patients. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BK virus-associated nephropathy has been observed during the use of mycophenolate mofetil in patients post-renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk of BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Blood and Immune System
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of mycophenolate mofetil therapy. In transplant patients however, reduced immunosuppression may place the graft at risk.

Patients receiving mycophenolate mofetil should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression. Patients on mycophenolate mofetil should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to mycophenolate mofetil, concomitant medications, viral infection or some combination of these causes. If neutropenia develops (absolute neutrophil count < 1.3 x 1 03/µL), dosing with mycophenolate mofetil should be interrupted or the dose reduced and the patient should be carefully observed.

0.5% of patients receiving mycophenolate mofetil 2 g for prevention of rejection in renal transplantation, 2.8% of patients receiving mycophenolate mofetil 3 g in cardiac transplantation and 3.6% of patients receiving mycophenolate mofetil 3 g in hepatic transplantation, developed severe neutropenia (absolute neutrophil count [ANC] < 5x108/L).

Patients should be advised that during treatment with mycophenolate mofetil vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see **Interactions with Other Medicines**). Influenza vaccination may be of value. Physicians should refer to the national guidelines for influenza vaccination.

Gastrointestinal
Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including uncommon cases of gastrointestinal tract ulceration, haemorrhage, and perforation (colon, gall bladder) in post- marketing surveillance, mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease. Gastrointestinal tract bleeding (requiring hospitalisation) has been observed in approximately 1.4% of patients treated with mycophenolate mofetil 2 g in renal transplantation, 2.8% of patients receiving 3 g in cardiac transplantation and in 5.4% of patients receiving mycophenolate mofetil 3 g in hepatic transplantation. Gastrointestinal tract perforations have rarely been observed. Most patients were also receiving other drugs that are associated with these complications (see **ADVERSE EFFECTS**). It should be noted that patients with active peptic ulcer disease were excluded from enrolment in studies with MMF.

Since mycophenolate mofetil is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, on

theoretical grounds it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions
Azathioprine: It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied.

Use in Patients with Severe Chronic Renal Impairment
Patients with severe chronic renal impairment (GFR < 25 mL/min/1 .73m2) who have received single doses of mycophenolate mofetil showed increased plasma AUCs of MPA and MPAG relative to patients with lesser degrees of renal impairment or normal healthy patients. Patients with severe chronic renal impairment should be carefully monitored and administration of doses of mycophenolate mofetil greater than 1 g bd should be avoided (Refer to **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**).

In patients with delayed graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2 - 3 fold higher, compared to that seen in post-transplant patients without delayed graft function. In the three controlled studies of prevention of rejection, there were 298 of 1,483 patients (20%) with delayed graft function. Although patients with delayed renal allograft function have a higher incidence of certain adverse events (anaemia, thrombocytopenia, hyperkalaemia) than patients without delayed graft function, these events were not more frequent in patients receiving mycophenolate mofetil than azathioprine or placebo. No dose adjustment is recommended for these patients, however, they should be carefully observed.

In renal transplant patients with severe chronic renal impairment, administration of doses greater than 1 g twice daily should be avoided.

Effects on Fertility
MMF had no effect on fertility of male rats at oral doses up to 20 mg/kg/day (0.8 times the expected maximum clinical dose based on AUC values). In a female fertility and reproduction study conducted in rats dosed orally at up to 4.5 mg/kg/day (0.1 times the maximum clinical dose based on AUC values), the 4.5 mg/kg/day dose caused malformations (principally of the head and eyes) in the first generation (F1) offspring in the absence of maternal toxicity. No effects on fertility were present in the treated females (P1 females), or in the subsequently mated first generation offspring (P2 females or P2 males).

Use in Pregnancy - Category D
Mycophenolate mofetil is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods (see **CONTRAINDICATIONS**).

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Prior to starting therapy with mycophenolate mofetil, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting mycophenolate mofetil. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.

Due to the mutagenic and teratogenic potential of mycophenolate mofetil, women of child bearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning mycophenolate mofetil therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception. Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients are recommended to use highly effective contraception during treatment and for total of 90 days after the last dose of mycophenolate mofetil.

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during

pregnancy. The following malformations were most frequently reported:

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

In the medical literature, malformations in children from mycophenolate mofetil exposed pregnancies have been reported in 23% to 27% of live births. For comparison the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosupressants other than mycophenolate mofetil.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate mofetil exposure, compared to a reported rate between 12% and 33% in solid organ transplant patients treated with other immunosuppressants.

In teratology studies, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (0.2 times the expected maximum human dose based on AUC values) and in rabbits at 90 mg/kg/day (0.1 times the expected maximum human dose based on AUC values), in the absence of maternal toxicity. The no-effect levels for teratologic changes in rats and rabbits were 2 and 30 mg/kg/day, respectively.

Use in Lactation
Mycophenolate mofetil is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see **CONTRAINDICATIONS**). Studies in rats have shown MMF to be excreted in milk. It is not known whether this medicine is excreted in human milk.

Paediatric Use
Based on a safety and pharmacokinetics study in renal paediatric patients, no significant differences in pharmacokinetic parameters in comparison to adult patients were observed. Paediatric patients experienced a higher incidence of certain adverse events (see **ADVERSE EFFECTS**). Data are insufficient to establish safety and efficacy in children below the age of two years.

Use in the Elderly
Elderly patients may be at an increased risk of adverse events such as certain infections (including CMV tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals. Elderly patients (over 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Pharmacokinetic behaviour of mycophenolate mofetil in the elderly has not been formally evaluated.

Genotoxicity
MMF did not induce point mutations (Ames assay) or primary DNA damage (yeast mitotic gene conversion assay) in the presence or absence of metabolic activation. MMF did not cause chromosomal damage *in vivo* at oral doses up to 3000 mg/kg (mouse micronucleus aberration assay) or *in vitro* with or without metabolic activation at concentrations up to 5 µg/mL (Chinese hamster ovary cell [CHO] chromosomal aberration assay). Chromosome aberrations were present without metabolic activation in an initial CHO cell assay, but only at concentrations (249 to 300 µg/mL) that cause excessive cytotoxicity.

Carcinogenicity
A 104-week oral carcinogenicity study in mice with MMF at daily doses of 25, 75 or 180 mg/kg showed an increase above control levels in the incidence of lymphosarcomas in females at the highest two dose levels and in males at the highest dose level (1.1-1.9 times the expected maximum clinical dose based on AUC values). The incidence of lymphosarcomas in all mice remained within the range of that observed historically in this strain of mice. In a 104- week oral carcinogenicity study in rats, MMF in daily doses up to 15 mg/kg (0.6 times the expected maximum clinical dose based on AUC values) was not tumourigenic.

The incidence of lymphoma/lymphoproliferative disease and other malignancies is also increased in

patients on immunosuppressive agents, and this appears to be related to the intensity or duration of immunosuppression rather than any specific immunosuppressant agent (see **PRECAUTIONS**).

INTERACTION WITH OTHER MEDICINES

Drug interaction studies with MMF have been conducted with aciclovir, antacids, cholestyramine, cyclosporin A, ganciclovir, oral contraceptives, proton pump inhibitors, tacrolimus and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other medicines that may be commonly administered to renal, cardiac or hepatic transplant patients.

Aciclovir: Following single dose administration of MMF (1 g) and aciclovir (800 mg) to normal healthy subjects, higher MPAG (8.6%) and aciclovir (17.4%) plasma AUCs were observed when MMF was administered with aciclovir in comparison to the administration of each drug alone. As MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for the mycophenolate mofetil and aciclovir or its prodrugs e.g. valaciclovir to compete for tubular secretion and thus further increases in concentrations of both drugs may occur.

Antacids with magnesium and aluminium hydroxides: Absorption of a single dose of MMF (2.0 g) was decreased when aluminium/magnesium hydroxide antacids were administered concomitantly to rheumatoid arthritis patients. The C_{max} and 24 hour AUC values for MPA were 33% and 17% lower, respectively than when MMF was administered alone under fasting conditions.

Cholestyramine: Following single dose administration of 1.5 g MMF in normal healthy subjects pretreated with 4 g tid of cholestyramine for 4 days, there was a mean 40% reduction in the AUC of MPA (see **Pharmacokinetics**). In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used with the concomitant use of mycophenolate mofetil and any drug which interferes with enterohepatic circulation because of the potential to reduce the efficacy of mycophenolate mofetil.

Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tended to diminish with continued antibiotic use and cease after discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure, therefore, clinical relevance of these observations is unclear.

Cyclosporin A: Cyclosporin A (CsA) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.0 g MMF bd in stable renal transplant patients. The mean (±SD) dose normalised $AUC_{0\text{-}12h}$ of MPA after 14 days and 3 months of multiple doses of mycophenolate mofetil and cyclosporin in 17 renal transplant patients were 43 ± 11 µg.h/mL.g and 56 ± 31 µg.h/mL.g, respectively.

Sirolimus: A study in 36 renal transplant patients demonstrated that concomitant administration of mycophenolate mofetil (1 g bd) and sirolimus resulted in the mean (± SD) $AUC_{0\text{-}12h}$ of MPA after 14 days and 3 months were 81 ± 36 and 71 ± 26 µg.h/mL.g respectively. Another study using 45 renal transplant patients demonstrated that significant proportion of patients (10 of 30) who received the combination of sirolimus and mycophenolate mofetil were withdrawn with symptoms consistent with MPA or sirolimus toxicity. Monitoring of MPA levels should be performed in renal graft recipients co-treated with sirolimus because of the risk of overexposure to this immunosuppressive agent.

Ganciclovir: Following single dose administration in stable renal transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and IV ganciclovir (5 mg/kg). However, as MPAG plasma and ganciclovir concentrations are increased in the presence of renal impairment, the potential exists for the two medicines to compete for tubular secretion, and thus further increases in concentrations of both medicines may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrugs (e.g. valganciclovir) are co-administered, patients should be carefully monitored. However with MPA no substantial alteration of MPA pharmacokinetics is anticipated and dose adjustment of MMF is not required.

Iron: In a study involving 16 healthy volunteers, no clinically relevant interaction was found between mycophenolate mofetil and iron supplements when administered in a fasting state. In the same study, a 15% reduction in MPA AUC was observed when mycophenolate mofetil and iron were administered

simultaneously with food. In an earlier study involving 7 healthy volunteers, a significant reduction in MPA AUC was observed when mycophenolate mofetil and iron were administered in a fasting state. To avoid any possible interactions, iron supplements should be administered at least 3 hours following mycophenolate mofetil.

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

Oral Contraceptives: The pharmacokinetics of oral contraceptives were unaffected by co-administration of mycophenolate mofetil. A study of co-administration of mycophenolate mofetil (1 g bd) and combined oral contraceptives containing ethinylestradiol (0.02 - 0.04 mg) and levonorgestrel (0.05 - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 - 0.1 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on serum levels of progesterone, LH and FSH, thus indicating no influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives (see **Use in Pregnancy**).

Proton Pump Inhibitors (PPIs): Decreased MPA exposure has been observed when PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and mycophenolate mofetil. Because clinical relevance has not been established, PPIs should be used with caution when co-administered to transplant patients being treated with mycophenolate mofetil.

Rifampicin: After correction for dose, a 70% decrease in MPA exposure (AUC_{0-12h}) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when the drugs are administered concomitantly.

Tacrolimus: The AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co- administration with tacrolimus, in stable hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1 .5g bd) were administered to patients taking tacrolimus.However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil.

Trimethoprim/Sulfamethoxazole: Following single dose administration of MMF (1.5 g) to healthy male volunteers pretreated for 10 days with trimethoprim 160 mg/sulfamethoxazole 800 mg, no effect on the bioavailability of MPA was observed.

Norfloxacin/Metronidazole: The combination of norfloxacin and metronidazole reduced the MPA AUC following a single dose of mycophenolate mofetil.

Sevelamer and Other Calcium-Free Phosphate Binders: Concomitant administration of sevelamer and mycophenolate mofetil in adults and paediatric patients decreased the C_{max} and AUC_{0-12} of MPA by 30% and 25% respectively. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer. This data suggest that sevelamer and other calcium- free phosphate binders should preferentially be given two hours after mycophenolate mofetil intake to minimise impact on the absorption of MPA.

Other Interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with MMF in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other medicines known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

ADVERSE EFFECTS

The adverse event profile associated with the use of immunosuppressive medicines is often difficult to establish owing to the presence of underlying disease and the concurrent use of many other medications. The principal adverse reactions associated with the administration of mycophenolate mofetil in combination with cyclosporin and steroids include diarrhoea, leukopenia, sepsis and

vomiting, and there is evidence of a higher frequency of certain types of infections, such as tuberculosis and atypical mycobacterial infection. Uncommon but serious life-threatening infections such as meningitis and infectious endocarditis have been reported.

The incidence of adverse events for mycophenolate mofetil was determined in 3 randomised comparative double blind trials in prevention of rejection in renal transplant patients. However, due to the lower overall reporting of events in the placebo-controlled prevention of rejection study, these data were not combined with the other two active-controlled prevention trials, but are instead presented separately.

Patients in the double blind studies of the prevention of renal allograft rejection were treated for up to a minimum of 1 year, with approximately 53% of the patients having been treated for more than 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the mycophenolate mofetil 2 g or 3 g treatment groups are presented below, for the two active-controlled studies combined, and for the one placebo-controlled study.

Adverse Events in Prevention of Renal Allograft Rejection

	Active – Controlled Studies			**Placebo – Controlled Studies**		
	Azathioprine 1-2 mg/kg per day or 100-150 mg/day (n=326) %	MMF 2 g/day (n=336) %	MMF 3 g/day (n=330) %	Placebo (n=166) %	MMF 2 g/day (n=165) %	MMF 3 g/day (n=160) %
Digestive System						
Diarrhoea	12.6	17.9	23.3	9.6	9.1	13.1
Constipation	11.0	12.2	7.9	1.2	3.0	1.3
Dyspepsia	8.9	10.4	7.3	1.8	1.2	0.6
Oral Moniliasis	11.0	9.8	12.1	6.6	6.1	3.1
Nausea	10.7	9.5	12.1	2.4	2.4	4.4
Nausea and Vomiting	7.7	6.0	5.2	1.2	0.6	0
Vomiting	4.6	5.1	4.8	1.2	1.2	1.9
Oesophagitis	2.1	4.2	4.8	0.6	0	0
Gastritis	0.6	4.2	3.0	1.2	1.2	2.5
Flatulence	3.4	3.9	1.8	0	1.8	0
Liver Function Tests	2.5	3.0	2.1	6.0	3.0	3.1
Gastrointestinal Moniliasis	1.8	3.0	2.4	0	1.8	1.3
Gastroenteritis	0.3	1.5	1.8	1.8	2.4	4.4
Infection	0.6	0.9	3.3	1.2	1.8	2.5
Body as a Whole						
Abdominal Pain	9.2	13.4	12.1	7.2	6.7	5.6
Sepsis	11.7	12.5	12.7	13.3	21.8	17.5
Infection	6.1	4.5	6.1	12.7	12.7	15.0
Fever	2.8	4.5	4.2	1.8	2.4	3.1
Headache	4.0	3.9	2.7	0.6	0	0
Pain	2.1	3.6	1.8	1.8	0.6	0.6
Flu Syndrome	0.6	0.9	0.6	2.4	3.6	5.0
Asthenia	1.8	1.8	3.0	0.6	0	0
Urogenital System						

Urinary Tract Infection	10.7	13.4	11.5	37.3	45.5	44.4
Pyelonephritis	0.3	0.3	0.3	3.0	3.6	1.9
Haemic and Lymphatic System						
Leucopenia	22.1	19.0	31.2	3.0	9.7	11.9
Thrombocytopenia	9.5	6.0	4.8	3.0	4.2	2.5
Anaemia	3.4	6.0	4.8	0.6	1.2	2.5
Leucocytosis	2.5	2.1	3.6	0	0	0.6
Respiratory System						
Infection	3.1	3.6	4.5	7.8	13.9	11.9
Pneumonia	1.2	2.1	1.5	10.8	3.6	10.6
Bronchitis	0.3	1.5	0.6	8.4	8.5	11.3
Pharyngitis	0.9	0.9	2.7	4.2	2.4	3.1
Metabolic and Nutritional Disorders						
Lactic Dehydrogenase Increased	4.9	5.1	5.2	0	0	0
Hypophosphataemia	4.3	5.4	5.2	0	0	0
SGPT Increased	2.8	3.9	3.0	1.2	1.2	1.9
Alkaline Phosphatase Increased	1.8	4.2	2.7	0.6	0	1.9
Hyperlipidaemia	3.1	3.3	3.0	0	0.6	0
SGOT Increased	1.5	2.7	3.3	0	0	0
Creatinine Increased	0.9	0.3	0.6	1.2	1.8	3.1

Patients in a double blind study of the prevention of cardiac allograft rejection were treated for up to a minimum of 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the mycophenolate mofetil 3 g or azathioprine treatment groups are presented below.

Adverse Events in Prevention of Cardiac Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active – Controlled Studies	
	MMF 3 g/day (n=289) %	Azathioprine 1.5-3 mg/kg/day (n=289) %
Digestive System		
Nausea	21.8	17.6
Diarrhoea	14.2	11.8
Oral Moniliasis	11.4	11.8
Vomiting	9.7	11.4
Dyspepsia	7.3	5.5
Constipation	5.5	6.6
Flatulence	3.1	5.5
Gastritis	5.2	2.8
Nausea and Vomiting	3.5	3.1
Anorexia	3.8	2.4
Liver Damage	3.1	3.1
Liver Function Tests Abnormal	3.1	2.1
Body as a Whole		

Sepsis	9.7	10.0
Headache	7.3	9.0
Abdominal Pain	7.6	7.3
Infection	8.7	5.9
Fever	1.0	3.1
Nervous System		
Insomnia	3.1	2.1
Urogenital System		
Urinary Tract Infection	4.2	4.5
Haemic and Lymphatic System		
Leucopenia	26.0	36.3
Anaemia	6.2	7.6
Thrombocytopenia	3.5	6.6
Respiratory System		
Infection	2.4	4.2
Pneumonia	1.7	3.1
Metabolic & Nutritional Disorders		
Bilirubinaemia	6.2	7.3
SGPT Increased	3.8	4.2
SGOT Increased	2.4	4.2
Alkaline Phosphatase Increased	2.4	3.8
Lactic Dehydrogenase Increased	2.8	3.5

Patients in a double blind study of the prevention of hepatic allograft rejection were followed for up to a minimum of 1 year. The adverse events reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the mycophenolate mofetil 3 g or azathioprine treatment groups are presented below.

Adverse Events in Prevention of Hepatic Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active – Controlled Studies	
	MMF 3 g/day (n=277) %	Azathioprine 1-2 mg/kg/day (n=287) %
Digestive System		
Diarrhoea	28.2	25.4
Nausea	26.7	19.9
Vomiting	11.9	12.2
Oral Moniliasis	9.4	9.8
Dyspepsia	6.5	10.1
Hepatitis	4.7	8.0
Anorexia	7.9	4.5
Constipation	5.4	4.5
Flatulence	5.4	3.1
Liver Function Tests Abnormal	4.0	3.1
Gastrointestinal moniliasis	2.5	4.2
Infection	3.2	2.8
Melaena	3.2	2.8

Haemic and Lymphatic System		
Leucopenia	42.2	35.2
Anaemia	12.6	19.9
Thrombocytopenia	14.4	16.0
Hypochromic anaemia	6.1	4.2
Leucocytosis	4.3	4.9
Body as a Whole		
Sepsis	18.8	20.2
Abdominal Pain	15.9	11.5
Fever	8.7	9.4
Infection	7.9	9.4
Headache	7.6	7.3
Peritonitis	3.2	4.9
Abdomen enlarged	4.0	3.5
Asthenia	2.2	3.1
Respiratory System		
Infection	4.0	6.6
Respiratory moniliasis	4.3	5.6
Pneumonia	4.7	2.4
Nervous System		
Insomnia	5.1	4.5
Tremor	3.6	2.1
Urogenital System		
Urinary Tract Infection	7.6	9.4
Cardiovascular System		
Hypertension	6.5	2.8
Skin and Appendages		
Herpes Simplex	9.4	5.6
Herpes Zoster	4.0	4.9

The following adverse events, considered by the investigator to be possibly or probably related to drug treatment and not mentioned in any of the tables above or in text pertaining to infections or malignancy following, were reported with an incidence of less than 3% in one or more of the mycophenolate mofetil 2 g or 3 g (renal) active-controlled cohorts (n = 336, n = 330), the mycophenolate mofetil 2 g or 3 g (renal) placebo-controlled cohorts (n = 165, n = 160), less than 1.4% in the mycophenolate mofetil 3 g (cardiac) active-controlled cohort (n = 289), or less than 1.4 % in the mycophenolate mofetil 3 g (hepatic) active-controlled cohort study (n = 277).

Digestive System*:* colitis (sometimes caused by cytomegalovirus), ileus, duodenal ulcer, rectal disorder, stomach ulcer, duodenitis, gastrointestinal haemorrhage, mouth ulceration, dysphagia, peptic ulcer, cholecystitis, gastrointestinal disorder, ulcerative stomatitis, cheilitis, large intestine perforation, periodontal abscess, haemorrhagic gastritis, gum hyperplasia, stomatitis, eructation, haemorrhagic pancreatitis, intestinal necrosis, intestinal perforation, intestinal ulcer, gingivitis, glossitis, oesophageal ulcer, pancreatitis, apthous stomatitis, enteritis, faecal impaction, stomach atony, haematemesis, duodenal ulcer haemorrhage, proctitis, rectal haemorrhage, gastrointestinal carcinoma, faecal incontinence, pancreas disorder, stomach ulcer haemorrhage, cholangitis, hepatic failure, perforated peptic ulcer, ulcerative colitis.

Body as a Whole: back pain, cyclosporin level increased, chest pain, reaction unevaluable, accidental injury, abscess, lab test abnormal, cyst, neoplasm, chills, face oedema, malaise, substernal chest pain, carcinoma, moniliasis, chills and fever, sarcoma, adenoma, granuloma, lack of drug effect, syncope, pelvis pain, pain, oedema, drug level increased, drug level decreased, injection site reaction, injection site

inflammation, injection site hypersensitivity.

Urogenital System: dysuria, cystitis, haematuria, infection, oliguria, urinary frequency, pyuria, kidney abscess, abnormal kidney function, urethritis, urogenital carcinoma, kidney pain, nephritis, urethral pain, urinary urgency, urinary tract disorder, hydronephrosis, epididymitis, kidney tubular necrosis, urogenital occlusion, bladder neoplasm, urinary incontinence, vaginal moniliasis, kidney failure, urine abnormality.

Reproductive System: vaginal moniliasis, metrorrhagia, prostatic disorder, amenorrhoea, balanitis, cervix disorder, endometrial carcinoma, vaginal haemorrhage, impotence, breast pain, gynaecomastia, penis disorder.

Skin and Appendages: alopecia, fungal dermatitis, skin benign neoplasm, rash, acne, cutaneous moniliasis, pruritus, infection, urticaria, cellulitis, sweating, haemorrhage (skin and appendages), vesiculobullous rash, skin disorder, skin hypertrophy, skin ulcer, furunculosis, injection site inflammation, maculopapular rash, petechial rash, seborrhoea, skin carcinoma, skin discolouration.

Haemic and Lymphatic System: pancytopenia, polycythemia, thrombocythemia, agranulocytosis, lymphoma like reaction, decreased immunoglobulins, ecchymosis, thrombotic thrombocytopenic purpura, epistaxis, haemorrhage, petechia, abnormal WBC, blood dyscrasia, haemolytic anaemia, lymphadenopathy, hepatitis B serum antigen positive, reticuloendothelial hyperplasia, marrow hyperplasia, coagulation disorder, haemolysis.

Respiratory System: sinusitis, cough increased, dyspnoea, rhinitis, respiratory abscess, interstitial pneumonia, lung carcinoma, lung disorder, asthma, laryngismus, laryngitis, pneumothorax, hypoxia, atelectasis, lung oedema, lung fibrosis, pleural effusion, pleural disorder.

Metabolic and Nutritional Disorders: gamma glutamyl transpeptidase increased, hypercholesterolaemia, hypokalaemia, acidosis, increased creatinine, bilirubinaemia, peripheral oedema, increased amylase, healing abnormal, hypocalcaemia, hyperglycaemia, albuminuria, weight loss, BUN increased, dehydration, decreased gamma globulin, hypercalcaemia, hypervolaemia, hypoproteinaemia, uremia, hyperkalaemia, hyperchloraemia, enzymatic abnormality, hypomagnesaemia, increased creatine phosphokinase, hyperuricaemia, hyponatraemia, diabetes mellitus, gout, respiratory acidosis, oedema, hypoglycaemia, cachexia, hyperphosphataemia.

Liver and Biliary System: liver damage, cholestatic jaundice, cholelithiasis.

Cardiovascular System: pulmonary embolus, thrombosis, palpitation, angina pectoris, vasodilatation, arterial thrombosis, cerebrovascular accident, phlebitis, atrial fibrillation, supraventricular tachycardia, cyanosis, cerebral ischaemia, hypotension, peripheral gangrene, tachycardia, arrhythmia, heart arrest, occlusion, shock, gangrene, deep thrombophlebitis, myocardial infarct, cardiomegaly, ventricular extrasystoles, ventricular tachycardia, cerebral ischaemia, myocarditis, endocarditis, heart failure, pulmonary hypertension, cardiomyopathy, electrocardiogram abnormal, pericardial effusion.

Central and Peripheral Nervous System: hypertonia, dizziness, anxiety, vocal cord paralysis, neuropathy, paraesthesia, convulsion, depression, confusion, amnesia, depersonalisation, encephalitis, psychosis, agitation, hallucinations, aphasia, delirium, encephalopathy, hyperaesthesia, nystagmus, speech disorder, thinking abnormal, vertigo, apathy, catatonic reaction, CNS neoplasia, delusions, hemiplegia, hostility, hypokinesia, opisthotonos, paranoid reaction, personality disorder, somnolence, hypesthesia, emotional lability, hyperkinesia, manic reaction.

Special Senses: otitis media, infection, conjunctivitis, eye haemorrhage, blepharitis, ear pain, visual disturbance, lacrimation disorder, corneal ulcer, deafness, diplopia, retinal disorder, taste loss, keratitis, retinitis, ear disorder, vestibular disorder, eye disorder, taste perversion, tinnitus, otitis externa, amblyopia, abnormal vision, eye pain, photophobia.

Musculo-Skeletal System: arthralgia, bone pain, leg cramps, myalgia, bone necrosis, joint disorder, myasthenia, myopathy, osteoporosis.

Endocrine: sialadenitis, hormone level altered hypothyroidism.

Up to 0.5% (regardless of investigator assessment of causality) of patients receiving mycophenolate mofetil 2 g for prevention of renal allograft rejection developed severe neutropenia (absolute neutrophil

count (ANC) < 5 x 108/L). Up to 2.8% (regardless of investigator assessment of causality) of cardiac transplant patients receiving mycophenolate mofetil 3 g and up to 3.6% (regardless of investigator assessment of causality) of patients receiving mycophenolate mofetil 3 g in hepatic transplantation developed severe neutropenia.

Cytomegalovirus (CMV) tissue invasive disease was more common in renal transplant patients receiving mycophenolate mofetil 3 g/day (8 - 12%) than in those receiving mycophenolate mofetil 2 g/day (4 - 8%) or control therapy (2 - 6%) in the three controlled studies for prevention of renal allograft rejection (percentage incidences have been determined regardless of investigator assessment of causality). In the placebo-controlled renal study, there was an increased incidence of *Herpes simplex* and *Herpes zoster* infections in patients receiving mycophenolate mofetil compared to placebo. In addition, the incidence of overall infection with Candida and CMV viraemia/syndrome were similar in the three treatment groups. The following tables show the incidence of select opportunistic infections in the prevention of rejection trials:

Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

	Renal Studies			**Cardiac Study**		**Hepatic Study**	
	MMF 2 g/day (n=336) %	MMF 3 g/day (n=330) %	Azathioprine 1 - 2mg/kg/day or 100-150 mg/day (n=326) %	MMF 3 g/day (n=289) %	Azathioprine 1.5 - 3 mg/kg/day or 100-150 mg/day (n=289) %	MMF 3 g/day (n=277) %	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=287) %
Herpes simplex	16.7	20.0	19.0	20.8	14.5	10.1	5.9
CMV							
Viraemia/syndrome	13.4	12.4	13.8	12.1	10.0	14.1	12.2
Tissue invasive disease	8.3	11.5	6.1	11.4	8.7	5.8	8.0
Herpes zoster	6.0	7.6	5.8	10.7	5.9	4.3	4.9
Cutaneous disease	6.0	7.3	5.5	10.0	5.5	4.3	4.9
Candida	17.0	17.3	18.1	18.7	17.6	22.4	24.4
Mucocutaneous	15.5	16.4	15.3	18.0	17.3	18.4	17.4

The following other opportunistic infections occurred with an incidence of less than 4% in mycophenolate mofetil patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease; Candida, urinary tract infection, fungemia/ disseminated disease, tissue invasive disease; Cryptococcosis; Aspergillus/Mucor; Pneumocystis carinii.

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal study, with a notably lower incidence of Herpes simplex and CMV tissue-invasive disease.

In the three controlled studies for prevention of rejection in renal transplantation, similar rates of fatal infections/sepsis (< 2%) have occurred in patients receiving mycophenolate mofetil or control therapy in combination with other immunosuppressive agents. In the controlled cardiac transplant study, fatal infections occurred in 2.4% of patients receiving mycophenolate mofetil 3 g compared to 4.5% of patients receiving azathioprine, both in combination with other immunosuppressive agents. In the controlled hepatic transplant study, fatal infection/sepsis occurred in 5.4% of patients receiving mycophenolate mofetil 3 g compared to 7.3% receiving azathioprine, both in combination with other immunosuppressive agents.

As with other patients receiving immunosuppressive regimes involving combinations of drugs, patients receiving mycophenolate mofetil as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. Within 3 years post transplant, lymphoproliferative disease or lymphoma developed in patients receiving mycophenolate mofetil in immunosuppressive regimes in 0.6% of patients receiving 2 g daily in the controlled studies of

prevention of renal rejection compared to placebo (0%) and azathioprine groups (0.6%).

The incidence of malignancies among the 1,483 patients enrolled in controlled trials for the prevention of renal allograft rejection was low, and similar to the incidence reported in the literature for renal allograft recipients. There was a slight increase in the incidence of lymphoproliferative disease in the MMF treatment groups compared to the placebo and azathioprine groups. The following table summarises the incidence of malignancies observed in the prevention of rejection trials.

Malignancies Observed in Prevention of Renal, Cardiac and Hepatic Rejection Trials
No. of patients (%) with one or more malignancies
(Regardless of Investigator Assessment of Causality)

	Renal Studies				Cardiac Study		Hepatic Study	
	Placebo (n=166) %	MMF 2 g/day (n=501) %	MMF 3 g/day (n=490) %	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326) %	MMF 3 g/day (n=289) %	Azathioprine 1.5 - 3 mg/kg/day (n=289) %	MMF 3 g/day (n=277) %	Azathioprine 1 - 2 mg/kg/day (n=287) %
Lymphoma/lympho-proliferative disease	0	0.6	1.0	0.3	0.7	2.1	0.4	0
Non-melanoma skin carcinoma	0	4.0	1.6	2.4	4.2	2.8	2.2	2.1
Other malignancy	1.8	0.8	1.4	1.8	2.1	2.1	0.7	2.4

Three year safety data in renal and cardiac transplant patients indicated that the overall incidence of malignancy was comparable between mycophenolate mofetil and azathioprine groups. Hepatic transplant patients were followed for at least 1 year but less than 3 years.

Paediatric Adverse Events
The type and frequency of adverse drug reactions in a clinical study of 100 paediatric patients 3 months to 18 years of age given 600 mg/m^2 MMF orally twice daily were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily with the exception that paediatric patients had a higher proportion of diarrhoea, anaemia, sepsis and leukopenia.

Post-Marketing Experience
Infections: uncommon serious life threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infections.

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in mycophenolate mofetil-treated patients. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function.

BK virus-associated nephropathy has been observed in patients treated with mycophenolate mofetil. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

Gastrointestinal: uncommon pancreatitis, isolated cases of intestinal villous atrophy, colitis (sometimes caused by cytomegalovirus).

Congenital Disorders: congenital malformations including ear malformations have been reported post marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy (see **Use in Pregnancy**).

Pregnancy, Puerperium and Perinatal Conditions
Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate mofetil have been reported (see Use in Pregnancy).

Blood and Immune System
Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents.

DOSAGE AND ADMINISTRATION

The initial dose of mycophenolate mofetil should be given as soon as clinically feasible following transplantation. Intravenous administration is recommended in those patients unable to take oral medication. However, oral administration should be initiated as soon as possible.

Note: Alternative preparations will be required for IV administration and dosages requiring an oral suspension.

Adults
Renal Transplantation
The recommended dose in renal transplant patients is 1 g administered orally or intravenously twice daily (2 g daily dose).

Cardiac Transplantation
The recommended dose in cardiac transplant patients is 1.5 g administered orally or intravenously twice daily (3 g daily dose).

Hepatic Transplantation
The recommended dose in hepatic transplant patients is 1 g administered intravenously twice daily (2 g daily dose) followed by 1.5 g administered orally twice daily (3 g daily dose).

Other Transplants
The recommended dose in other transplants is 2 to 3g per day depending on the level of immunosuppression required.

Paediatrics (2 to 18 years)
The recommended dose for renal transplant patients is 600 mg/m2 of MMF administered orally twice daily (up to a maximum of 2 g daily).

Mycophenolate mofetil may be administered in combination with cyclosporin and corticosteroids.

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (ANC < 1 .3x10^9/L), dosing with mycophenolate mofetil should be interrupted and the patient carefully observed (Refer to **PRECAUTIONS**).

Patients should be advised to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

In renal transplant patients with severe chronic renal impairment (GFR < 25 mL/min/1 .73m2) outside of the immediate post-transplant period, doses of mycophenolate mofetil greater than 1 g administered twice a day should be avoided. No data are available in cardiac or hepatic allograft recipients with severe chronic renal impairment. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal allograft function postoperatively.

No dosage adjustment is required in the elderly or in renal transplant patients with hepatic parenchymal disease.

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Handling and Disposal
As mycophenolate mofetil has demonstrated teratogenic effects in rat and rabbits studies, mycophenolate mofetil tablets should not be crushed and mycophenolate mofetil capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in mycophenolate mofetil capsules. If contact occurs, wash thoroughly with soap and water; should the eyes be affected, rinse eyes with plain water.

OVERDOSAGE

Reports of overdoses with MMF have been received from clinical trials and during post-marketing experience. In many of these cases no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the drug.

It is expected that an overdose of MMF could possibly result in over-suppression of the immune system and increase susceptibility to infections and bone marrow suppression (see **PRECAUTIONS**). If neutropenia develops, dosing with mycophenolate mofetil should be interrupted or the dose reduced (see **PRECAUTIONS**).

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/ml), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, can remove MPA by increasing excretion of the drug (see **Pharmacokinetics**).

Treatment of overdosage should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia)

PRESENTATION AND STORAGE CONDITIONS

APO-Mycophenolate capsules are intended for oral administration.

Each capsule contains 250 mg mycophenolate mofetil as the active ingredient

250 mg capsules:
Opaque blue cap and opaque pink body in Size 1 capsules containing white to off white powder. "M250" and "APO" are imprinted on capsules in black ink.
Blister pack (PVC/PVDC/Aluminium foil) of 100 and 300 capsules (AUST R 168109)
Bottles pack (HDPE bottle with a blue PP lift N peel cap closure) of 100, 300 and 500 capsules (AUST R 168108)

Not all pack types and/or pack sizes may be available

Storage
Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park, NSW 2113
Australia

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POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 8 November 2011

Date of most recent amendment: 18 January 2016