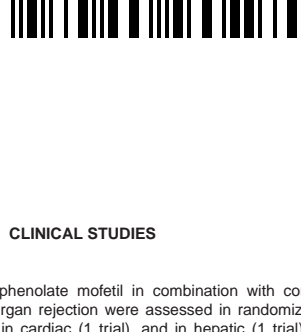


**MPACPHENOLATE MOFETIL Capsules and Tablets**

Roche Laboratories, Inc.  
Columbus, Ohio 43216

10004767101



Rx only

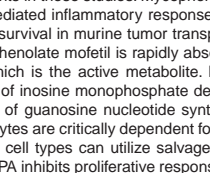
**WARNING**

**Immunosuppression may lead to increased susceptibility to infection and the possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use mycophenolate mofetil. Patients receiving the drug 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.**

**Female users of childbearing potential must use contraception. Use of mycophenolate mofetil during pregnancy is associated with increased risk of pregnancy loss and congenital malformations.**

**DESCRIPTION**

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent, inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuran-4-yl)-4-methyl-4-hexenoate. It has a molecular formula of C<sub>23</sub>H<sub>31</sub>NO<sub>7</sub>, a molecular weight of 433.5, and the following structural formula:



Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 mcg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

Mycophenolate is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/mL mycophenolate mofetil.

Inactive ingredients in Mycophenolate Mofetil Capsules, 250 mg include croscarmellose sodium, magnesium stearate, povidone, pregelatinized starch and purified water. The capsule shells contain FD&C blue #1, FD&C blue #3, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

Inactive ingredients in Mycophenolate Mofetil Tablets, 500 mg include croscarmellose sodium, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, polydextrose, povidone, pregelatinized starch, titanium dioxide, and triacetin.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Mycophenolate mofetil 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).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative activity in experimental models of aortic and cardiac allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allosteric stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil 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.

**Pharmacokinetics**

Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 mcg/mL).

**Absorption:** In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to intravenous mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see **Table 1**).

**Food** (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA C<sub>max</sub> was decreased by 40% in the presence of food (see **DOSE AND ADMINISTRATION**).

**Distribution:** The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (±1.5) and 4 (±1.2) L/kg following intravenous and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed renal graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

**In vitro** studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and urea (at ≥60 mg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 mcg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

**Metabolism:** Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. *In vivo*, MPA is converted to MPA via enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recorded in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency (see **CLINICAL PHARMACOLOGY: Special Populations**).

**Excretion:** Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 mcg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see **OVERDOSAGE**).

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration, respectively.

**Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant Patients:** Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac, and hepatic transplant patients. In the early posttransplant period (<40 days post-transplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C<sub>max</sub> approximately 32% to 44% lower compared to the late transplant period (3 to 6 months posttransplant).

Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid intravenous mycophenolate mofetil followed by 1.5 g bid oral mycophenolate mofetil resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g bid mycophenolate mofetil bid.

**Table 1: Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose), Renal, Cardiac, and Hepatic Transplant Patients (Multiple Doses)**

	Dose/Route	T <sub>max</sub> (h)	C <sub>max</sub> (mcg/mL)	Total AUC (mcg•h/mL)
<b>Healthy Volunteers (single dose)</b>	1 g/oral	0.8 (±0.36) (N=129)	24.5 (±9.5) (N=129)	63.9 (±16.2) (N=117)
<b>Renal Transplant Patients (bid dosing) Time After Transplantation</b>	Dose/Route	T <sub>max</sub> (h)	C <sub>max</sub> (mcg/mL)	Interdosing Interval AUC(0-12h) (mcg•h/mL)
5 days	1 g/iv	1.58 (±0.46) (N=31)	12 (±3.82) (N=31)	40.8 (±11.4) (N=31)
6 days	1 g/oral	1.33 (±1.05) (N=31)	10.7 (±4.83) (N=31)	32.9 (±15) (N=31)
Early (<40 days)	1 g/oral	1.31 (±0.76) (N=25)	8.16 (±4.5) (N=25)	27.3 (±10.9) (N=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (N=27)	13.5 (±8.18) (N=27)	38.4 (±15.4) (N=27)
Late (>3 months)	1.5 g/oral	0.9 (±0.24) (N=23)	24.1 (±12.1) (N=23)	65.3 (±35.4) (N=23)
<b>Cardiac Transplant Patients (bid dosing) Time After Transplantation</b>	Dose/Route	T <sub>max</sub> (h)	C <sub>max</sub> (mcg/mL)	Interdosing Interval AUC(0-12h) (mcg•h/mL)
Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (N=11)	11.5 (±5.8) (N=11)	45.3 (±20.8) (N=9)
Late (>6 months)	1.5 g/oral	(±0.7) (N=52)	(±9.4) (N=52)	(±4.14) (N=49)
<b>Hepatic Transplant Patients (bid dosing) Time After Transplantation</b>	Dose/Route	T <sub>max</sub> (h)	C <sub>max</sub> (mcg/mL)	Interdosing Interval AUC(0-12h) (mcg•h/mL)
4 to 9 days	1 g/iv	1.5 (±0.517) (N=22)	17 (±12.7) (N=22)	34 (±17.4) (N=22)
Early (5 to 8 days)	1.5 g/oral	1.15 (±0.432) (N=20)	13.1 (±6.76) (N=20)	29.2 (±11.9) (N=20)
Late (>6 months)	1.5 g/oral	1.54 (±0.51) (N=6)	19.3 (±11.7) (N=6)	49.3 (±14.8) (N=6)

<sup>a</sup> AUC (0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules. Five mL of the 200 mg/mL constituted oral suspension have been shown to be bioequivalent to four 250 mg capsules.

**Special Populations:** Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

**Table 2: Pharmacokinetic Parameters for MPA [mean (±SD)] Following Single Doses of Mycophenolate Mofetil Capsules in Chronic Renal and Hepatic Impairment**

Renal Impairment (no. of patients)	Dose	T <sub>max</sub> (h)	C <sub>max</sub> (mcg/mL)	AUC (0-96h) (mcg•h/mL)
Healthy Volunteers	1 g	0.75 (±0.27)	25.3 (±7.99)	45 (±22.6)
GFR >80 mL/min/1.73 m <sup>2</sup> (N=6)	1 g	0.75 (±0.27)	26 (±3.82)	59.9 (±12.9)
Mild Renal Impairment	1 g	0.75 (±0.27)	19 (±13.2)	52.9 (±25.5)
GFR 50 to 80 mL/min/1.73 m <sup>2</sup> (N=6)	1 g	1 (±1)	16.3 (±10.8)	78.6 (±46.4)
Moderate Renal Impairment	1 g	0.75 (±0.41)	24.3 (±10.8)	29 (±5.78)
GFR 25 to 49 mL/min/1.73 m <sup>2</sup> (N=6)	1 g	0.63 (±0.14)	23.3 (±7.4)	29 (±5.78)
Severe Renal Impairment	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)
GFR <25 mL/min/1.73 m <sup>2</sup> (N=7)	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

**Renal Insufficiency:** In a single-dose study, MMF was administered as capsule or intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m<sup>2</sup>] was about 75% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m<sup>2</sup>). In addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers (N=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m<sup>2</sup>) was 62.4 mcg•h/mL (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see **PRECAUTIONS: General and DOSAGE AND ADMINISTRATION**).

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable to that seen in posttransplant patients without delayed renal graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2-fold to 3-fold higher than in posttransplant patients without delayed renal graft function (see **PRECAUTIONS: General and DOSAGE AND ADMINISTRATION**).

In 8 patients with primary graft non-function following renal transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold.

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 mcg/mL), hemodialysis removes only small amounts of MPAG.

**Hepatic Insufficiency:** In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies. Thus, making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g intravenous) study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 mcg•h/mL (±15.5).

**Pediatrics:** The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving mycophenolate mofetil oral suspension at a dose of 600 mg/m<sup>2</sup> bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in **Table 3**.

**Table 3: Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Renal Transplantation**

Age Group (N)	Time	T <sub>max</sub> (h)	Dose Adjusted C <sub>max</sub> (mcg/mL)	Dose Adjusted AUC <sub>0-12h</sub> (mcg•h/mL)
1 to <2 yr (6) <sup>b</sup>	Early (Day 7)	3.03 (4.7)	10.3 (5.8)	22.5 (6.6)
1 to <6 yr (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to <12 yr (21)		0.94 (0.546)	13.1 (6.3)	26.2 (12.1)
12 to 18 yr (16)		1.16 (0.83)	11.7 (10.7)	33.3 (9.14)
1 to <2 yr (4) <sup>b</sup>	Late (Month 3)	0.989 (0.571)	23.8 (13.4)	47.4 (14.7)
1 to <6 yr (15)		0.289 (0.216)	22.7 (10.1)	49.7 (18.2)
6 to <12 yr (14)		1.21 (0.532)	27.8 (14.3)	61.9 (19.6)
12 to 18 yr (17)		0.978 (0.484)	17.9 (9.57)	53.6 (20.3)
1 to <2 yr (4) <sup>b</sup>	Late (Month 9)	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to <6 yr (12)		1.162 (0.479)	30.4 (12.6)	61 (10.7)
6 to <12 yr (11)		0.89 (0.462)	29.2 (9.6)	66.8 (21.2)
12 to 18 yr (14)		1.09 (0.518)	18.1 (7.59)	56.7 (14)

<sup>a</sup> Adjusted to a dose of 600 mg/m<sup>2</sup>  
<sup>b</sup> A subset of 1 to <6 yr  
<sup>c</sup> N=20  
<sup>d</sup> N=16

The mycophenolate mofetil oral suspension dose of 600 mg/m<sup>2</sup> bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving mycophenolate mofetil capsules at a dose of 1 g bid in the early post-transplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45% to 53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1 year to 18 year age range.

**Gender:** Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC(0-12h) for the males (N=79) was 32 (±14.5) and for females (N=41) was 36.5 (±18.8) mcg•h/mL while mean (±SD) MPA C<sub>max</sub> was 9.96 (±6.19) in the males and 10.6 (±5.64) mcg/mL in the females. These differences are not of clinical significance.

**Geriatrics:** Pharmacokinetics in the elderly have not been studied.

**CLINICAL STUDIES**

**Adults**

The safety and efficacy of mycophenolate mofetil in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients.

**Renal Transplant:** Adults: The three renal studies compared two dose levels of oral mycophenolate mofetil (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®) and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). Mycophenolate mofetil, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

Mycophenolate mofetil, in combination with corticosteroids and cyclosporine reduced (statistically significant at 0.05 level) the incidence of treatment failure within the first 6 months following transplantation. **Table 4** and **Table 5** summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving mycophenolate mofetil discontinued without prior biopsy-proven rejection, death or graft loss than discontinued in the control groups, with the highest rate in the mycophenolate mofetil 3 g/day group. Therefore, the acute rejection rates may be underestimated, particularly in the mycophenolate mofetil 3 g/day group.

**Table 4: Renal Transplant Studies Incidence of Treatment Failure (Biopsy-Proven Rejection or Early Termination for Any Reason)**

USA Study <sup>a</sup> (N=499)	Mycophenolate Mofetil 2 g/day (N=167)	Mycophenolate Mofetil 3 g/day (N=166)	Azathioprine 1 to 2 mg/kg/day (N=166)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection <sup>b</sup>	9.6%	12.7%	6%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38%
Europe/Canada/Australia Study <sup>c</sup> (N=503)	Mycophenolate Mofetil 2 g/day (N=163)	Mycophenolate Mofetil 3 g/day (N=164)	Azathioprine 100 to 150 mg/day (N=166)
All treatment failures	38.2%	34.8%	50%
Early termination without prior acute rejection <sup>b</sup>	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study <sup>d</sup> (N=491)	Mycophenolate Mofetil 2 g/day (N=165)	Mycophenolate Mofetil 3 g/day (N=160)	Placebo (N=166)
All treatment failures	30.3%	38.8%	56%
Early termination without prior acute rejection <sup>b</sup>	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17%	13.8%	46.4%

<sup>a</sup> Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.  
<sup>b</sup> Does not include death and graft loss as reason for early termination.  
<sup>c</sup> MMF or azathioprine/cyclosporine/corticosteroids.  
<sup>d</sup> MMF or placebo/cyclosporine/corticosteroids.

The cumulative incidence of 12-month graft loss or patient death is presented below. No advantage of mycophenolate mofetil with respect to graft loss or patient death was established. Numerically, patients receiving mycophenolate mofetil 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving mycophenolate mofetil 2 g/day experienced a better outcome than mycophenolate mofetil 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss or patient death at 1 year.

**Table 5: Renal Transplant Studies Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months**

Study	Mycophenolate Mofetil 2 g/day	Mycophenolate Mofetil 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11%	13.8%
Europe	8.5%	10%	11.5%

**Pediatrics:** One open-label, safety and pharmacokinetic study of mycophenolate mofetil oral suspension 600 mg/m<sup>2</sup> bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. Mycophenolate mofetil was well tolerated in pediatric patients (see **ADVERSE REACTIONS**), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid mycophenolate mofetil capsules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

**Cardiac Transplant:** A double-blind, randomized, comparative, parallel-group, multicenter study in primary cardiac transplant recipients was performed at 20 centers in the United States, 1 in Canada, 5 in Europe and 2 in Australia. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received mycophenolate mofetil 1.5 g bid (N=289) or azathioprine 1.5 to 3 mg/kg/day (N=289), in combination with cyclosporine (Sandimmune® or Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were retransplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

(1) **Rejection:** No difference was established between mycophenolate mofetil and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise.  
(2) **Survival:** Mycophenolate mofetil was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year (see **Table 6**).

**Table 6: Rejection at 6 Months/Death or Retransplantation at 1 Year**

	All Patients		Treated Patients	
	AZA (N=323)	Mycophenolate Mofetil (N=327)	AZA (N=289)	Mycophenolate Mofetil (N=289)
Biopsy-proven rejection with hemodynamic compromise at 6 months <sup>a</sup>	121 (38%)	120 (37%)	100 (35%)	92 (32%)
Death or retransplantation at 1 year	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

<sup>a</sup> Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥20 mm or a 25% increase; cardiac index <2 L/min/m<sup>2</sup> or a 25% decrease; ejection fraction ≤30%; pulmonary artery oxygen saturation ≤60% or a 25% decrease; presence of new S<sub>3</sub> gallop; fractional shortening was ≤20% or a 25% decrease; inotropic support required to manage the clinical condition

**Hepatic Transplant:** A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The

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

During treatment with mycophenolate mofetil, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: Drug Interactions: Live Vaccines**).

**Phenylketonurics**

Mycophenolate mofetil oral suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Therefore, care should be taken if mycophenolate mofetil oral suspension is administered to patients with phenylketonuria.

**Information for Patients**

- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking mycophenolate mofetil.
- Inform women of childbearing potential that use of mycophenolate mofetil in pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of birth defects, and that they must use effective contraception.
- Discuss pregnancy plans with female patients of childbearing potential.
  - Any female of childbearing potential must use highly effective (two methods) contraception 4 weeks prior to starting mycophenolate mofetil therapy and continue contraception until 6 weeks after stopping mycophenolate mofetil treatment, unless abstinence is the chosen method (see **WARNINGS: Pregnancy**).
  - A patient who is planning a pregnancy should not use mycophenolate mofetil unless she cannot be successfully treated with other immunosuppressant drugs.

**Laboratory Tests**

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 (see **WARNINGS, ADVERSE REACTIONS AND DOSAGE AND ADMINISTRATION**).

**Drug Interactions**

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. Mycophenolate mofetil has not been administered concomitantly with azathioprine.

**Acyclovir:** Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and C<sub>max</sub>. However, MPAG plasma concentrations were increased 10.6% and 21.3%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

**Antacids With Magnesium and Aluminum Hydroxides:** Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox<sup>®</sup> TC (10 mL qid). The C<sub>max</sub> and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. Mycophenolate mofetil may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that mycophenolate mofetil and the antacid not be administered simultaneously.

**Cholestyramine:** Following single-dose administration of 1.5 g mycophenolate mofetil to 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of mycophenolate mofetil. Therefore, mycophenolate mofetil is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

**Cyclosporine:** Cyclosporine (Sandimmune<sup>®</sup>) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10 stable renal transplant patients. The mean (±SD) MPA AUC(0-12h) and C<sub>max</sub> of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil.

In renal transplant patients, mean MPA exposure (AUC<sub>0-12h</sub>) was approximately 30 to 50% greater when mycophenolate mofetil is administered without cyclosporine compared with when mycophenolate mofetil is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

**Ganciclovir:** Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and C<sub>max</sub> (N=10) were 54.3 (±1.9) mcg•h/mL and 11.5 (±1.8) mcg/mL, respectively, after coadministration of the two drugs, compared to 51 (±1.7) mcg•h/mL and 10.6 (±2) mcg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and C<sub>max</sub> of MPA (N=12) after coadministration were 80.9 (±21.6) mcg•h/mL and 27.8 (±13.9) mcg/mL, respectively, compared to values of 80.3 (±16.4) mcg•h/mL and 30.9 (±11.2) mcg/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

**Oral Contraceptives:** A study of coadministration of mycophenolate mofetil (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.2 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.1 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. Mycophenolate mofetil may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives be coadministered with mycophenolate mofetil with caution and additional birth control methods be considered (see **WARNINGS: Pregnancy**).

**Sevelamer:** Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C<sub>max</sub> and AUC<sub>0-12h</sub>, by 36% and 26% respectively. This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with mycophenolate mofetil. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after mycophenolate mofetil intake to minimize the impact on the absorption of MPA.

**Trimethoprim/Sulfamethoxazole:** Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered bid, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and C<sub>max</sub> of MPA after concomitant administration were 75.2 (±19.8) mcg•h/mL and 34 (±6.6) mcg/mL, respectively, compared to 79.2 (±27.9) mcg•h/mL and 34.2 (±10.7) mcg/mL, respectively, after administration of mycophenolate mofetil alone.

**Norfloxacin and Metronidazole:** Following single-dose administration of mycophenolate mofetil (1 g) to 11 healthy volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole, the mean MPA AUC<sub>0-48h</sub> was significantly reduced by 33% compared to the administration of mycophenolate mofetil alone (p<0.05). Therefore, mycophenolate mofetil is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA AUC<sub>0-48h</sub> when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. The mean (±SD) MPA AUC<sub>0-48h</sub> after coadministration of mycophenolate mofetil with norfloxacin or metronidazole separately was 48.3 (±24) mcg•h/mL and 42.7 (±23) mcg•h/mL, respectively, compared with 56.2 (±24) mcg•h/mL after administration of mycophenolate mofetil alone.

**Rifampin:** In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure (AUC<sub>0-12h</sub>) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, mycophenolate mofetil is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

**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, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

**Live Vaccines:** During treatment with mycophenolate mofetil, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: General**). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see **WARNINGS**).

The genotoxic potential of mycophenolate mofetil was determined in five assays. Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay and the *in vivo* mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosome aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

**Pregnancy**

**Teratogenic Effects: Pregnancy Category D:** See **WARNINGS** section.

**Nursing Mothers**

Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of mycophenolate mofetil oral suspension is 600 mg/m<sup>2</sup> bid (up to a maximum of 1 g bid). Also see **CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS, AND DOSAGE AND ADMINISTRATION**.

**Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.**

**Geriatric Use**

Clinical studies of mycophenolate mofetil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see **ADVERSE REACTIONS**).

**ADVERSE REACTIONS**

The principal adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection (see **WARNINGS: Infections and WARNINGS: Progressive Multifocal Leukoencephalopathy (PML)**). The adverse event profile associated with the administration of mycophenolate mofetil (PML) has been shown to be similar to that observed after administration of oral dosage forms of mycophenolate mofetil.

The incidence of adverse events for mycophenolate mofetil was determined in randomized, comparative, double-blind trials in prevention of rejection in renal (2 active, 1 placebo-controlled trials), cardiac (1 active-controlled trial), and hepatic (1 active-controlled trial) transplant patients. **Geriatrics:** Elderly patients (>65 years), particularly those who are receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus [CMV] tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see **PRECAUTIONS**).

Safety data are summarized below for all active-controlled trials in renal (2 trials), cardiac (1 trial), and hepatic (1 trial) transplant patients. Approximately 53% of the renal patients, 65% of the cardiac patients, and 48% of the hepatic patients have been treated for more than 1 year. Adverse events reported in ≥20% of patients in the mycophenolate mofetil treatment groups are presented below.

**Table 8: Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥20% of Patients in the Mycophenolate Mofetil Group)**

	Renal Studies			Cardiac Study			Hepatic Study		
	Mycophenolate 2 g/day (N=336)	Mycophenolate 3 g/day (N=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (N=326)	Mycophenolate 3 g/day (N=289)	Azathioprine 1.5 to 3 mg/kg/day (N=289)	Mycophenolate 3 g/day (N=277)	Azathioprine 1 to 2 mg/kg/day (N=287)		
<b>Body as a Whole</b>									
Pain	33	31.2	32.2	75.8	74.7	74	77.7		
Abdominal Pain	24.7	27.6	23	33.9	33.2	62.5	51.2		
Fever	21.4	23.3	23.3	47.4	46.4	52.3	56.1		
Headache	21.1	16.1	21.2	54.3	51.9	53.8	49.1		
Infection	18.2	20.9	19.9	25.6	19.4	27.1	25.1		
Sepsis	-	-	-	-	-	27.4	26.5		
Asthenia	-	-	-	43.3	36.3	35.4	33.8		
Chest Pain	-	-	-	26.3	26	-	-		
Back Pain	-	-	-	34.6	28.4	46.6	47.4		
Asticles	-	-	-	-	-	24.2	22.6		
<b>Hemic and Lymphatic</b>									
Anemia	25.6	25.8	23.6	42.9	43.9	43	53		
Leukopenia	23.2	34.5	24.8	30.4	39.1	45.8	39		
Thrombocytopenia	-	-	-	23.5	27	36.3	42.3		
Hypocalcemia	-	-	-	24.6	23.5	27.1	25.1		
Leukocytosis	-	-	-	40.5	35.6	22.4	21.2		
<b>Urogenital</b>									
Urinary Tract Infection	37.2	37	33.7	-	-	-	-		
Kidney Function Abnormal	-	-	-	21.8	26.3	25.6	28.9		
<b>Cardiovascular</b>									
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6		
Hypotension	-	-	-	32.5	36	-	-		
Cardiovascular Disorder	-	-	-	25.6	24.2	-	-		
Tachycardia	-	-	-	20.1	18	22	17.7		
<b>Metabolic and Nutritional</b>									
Peripheral Edema	28.6	27	28.2	64	53.3	48.4	45.7		
Hypercholesterolemia	-	-	-	41.2	38.4	-	-		
Edema	-	-	-	26.2	25.6	28.2	28.2		
Hypokalemia	-	-	-	31.8	25.6	37.2	41.1		
Hyperkalemia	-	-	-	46.7	52.6	43.7	48.8		
Hypoglycemia	-	-	-	39.4	36	-	-		
Creatinine Increased	-	-	-	34.6	32.5	-	-		
BUN Increased	-	-	-	23.2	17	-	-		
Lactic Dehydrogenase Increased	-	-	-	-	-	39	37.6		
Hypocalcemia	-	-	-	-	-	30	30		
<b>Diarrhea</b>									
Diarrhea	31	36.1	20.9	45.3	34.3	51.3	49.8		
Constipation	22.9	18.5	22.4	41.2	37.7	37.9	38.3		
Nausea	19.9	23.6	24.5	54	54.3	54.5	51.2		
Dyspepsia	-	-	-	-	-	22.4	20.9		
Vomiting	-	-	-	33.9	28.4	32.9	33.4		
Anorexia	-	-	-	30.1	28.1	25.3	17.1		
Loss of Appetite	-	-	-	26	19	-	-		
<b>Laboratory Tests Abnormal</b>									
<b>Respiratory</b>									
Infection	22	23.9	19.6	37	35.3	-	-		
Dyspnea	-	-	-	36.7	36.3	31	30.3		
Cough Increased	-	-	-	31.1	25.6	-	-		
Lung Disorder	-	-	-	30.1	28.1	32	18.9		
Sinusitis	-	-	-	26	19	-	-		
Pleural Effusion	-	-	-	-	-	24.3	35.8		
<b>Skin and Appendages</b>									
Rash	-	-	-	22.1	18	-	-		
<b>Nervous System</b>									
Tremor	-	-	-	24.2	23.9	33.9	35.5		
Insomnia	-	-	-	40.8	37.7	52.3	47		
Dizziness	-	-	-	28.7	27.7	-	-		
Anxiety	-	-	-	28.4	23.9	-	-		
Parosmia	-	-	-	20.6	18	-	-		

The placebo-controlled renal transplant study generally showed fewer adverse events occurring in ≥20% of patients. In addition, those that occurred were not only qualitatively similar to the azathioprine-controlled renal transplant studies, but also occurred at lower rates, particularly for infection, leukopenia, hypertension, diarrhea and respiratory infection.

The above data demonstrate that in three controlled trials for prevention of renal rejection, patients receiving 2 g/day of mycophenolate mofetil had an overall better safety profile than did patients receiving 3 g/day of mycophenolate mofetil.

The above data demonstrate that the types of adverse events observed in multicenter controlled trials in renal, cardiac, and hepatic transplant patients are qualitatively similar except for those that are unique to the specific organ involved.

Sepsis, which was generally CMV viremia, was slightly more common in renal transplant patients treated with mycophenolate mofetil compared to patients treated with azathioprine. The incidence of sepsis was comparable in mycophenolate mofetil and in azathioprine-treated patients in cardiac and hepatic studies.

In the digestive system, diarrhea was increased in renal and cardiac transplant patients receiving mycophenolate mofetil compared to patients receiving azathioprine, but was comparable in hepatic transplant patients treated with mycophenolate mofetil or azathioprine.

Patients receiving mycophenolate mofetil alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **WARNINGS: Lymphoma and Malignancy**). The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥1 year was similar to the incidence reported in the literature for renal allograft recipients.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see **WARNINGS: Lymphoma and Malignancy**). Non-melanoma skin carcinomas occurred in 1.6% to 4.2% of patients, other types of malignancy in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data.

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

Severe neutropenia (ANC <0.5 x 10<sup>3</sup>/mL) developed in up to 2% of renal transplant patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant patients receiving mycophenolate mofetil 3 g daily (see **WARNINGS: Neutropenia, PRECAUTIONS: Laboratory Tests and DOSAGE AND ADMINISTRATION**).

All transplant patients are at increased risk of opportunistic infections. The risk increases with total immunosuppressive load (see **WARNINGS: Infections and WARNINGS: Progressive Multifocal Leukoencephalopathy (PML)**). Table 9 shows the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials:

**Table 9: Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection**

	Renal Studies			Cardiac Study			Hepatic Study		
	Mycophenolate 2 g/day (N=336)	Mycophenolate 3 g/day (N=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (N=326)	Mycophenolate 3 g/day (N=289)	Azathioprine 1.5 to 3 mg/kg/day (N=289)	Mycophenolate 3 g/day (N=277)	Azathioprine 1 to 2 mg/kg/day (N=287)		
Herpes simplex	16.7	20	19	20.8	14.5	10.1	5.9		
CMV									
Viremia/syndrome	13.4	12.4	13.8	12.1	10	14.1	12.2		
Tissue invasive disease	8.3	11.5	6.1	11.4	8.7	5.8	8		
Herpes zoster	6	7.6	5.8	10.7	5.9	4.3	4.9		
Cytomegalovirus	6	7.3	5.5	10	5.5	4.3	4.9		
Candida									

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NDC 0054-0163-29

500 Capsules

**MYCOPHENOLATE  
MOFETIL  
Capsules**

**250 mg**

Each capsule contains 250 mg  
mycophenolate mofetil.

**USUAL DOSAGE:** For dosage  
recommendations and other  
important prescribing information,  
read accompanying insert.

R<sub>x</sub> only



Boehringer Ingelheim  
Roxane Laboratories

10004764/01  
© RLI, 2006

Caution: Special Handling and  
Disposal instructions see insert.



LOT  
EXP.

Dispense in tight, light-resistant  
container as defined in the USP with  
a child-resistant cap.

Store at 25°C (77°F). See USP  
Controlled Room Temperature;  
excursions permitted to 15° to 30°C  
(59° to 86°F).

Roxane Laboratories, Inc.  
Columbus, Ohio 43216

This label may not be the latest approved by FDA.  
For current labeling information, please visit <https://www.fda.gov/drugs>

Dispense in tight,  
light-resistant container  
as defined in the USP  
with a child-resistant cap.

Store at 25°C (77°F). See  
USP Controlled Room  
Temperature; excursions  
permitted to 15° to 30°C  
(59° to 86°F).

Caution: Special Handling  
and Disposal instructions  
see insert.

Roxane Laboratories, Inc.  
Columbus, Ohio 43216

NDC 0054-0163-23 120 Capsules

**MYCOPHENOLATE  
MOFETIL  
Capsules**

**250 mg**

Each capsule contains 250 mg  
mycophenolate mofetil.

USUAL DOSAGE: For dosage  
recommendations and other  
important prescribing  
information, read  
accompanying insert.

R<sub>x</sub> only



Boehringer Ingelheim  
Roxane Laboratories

EXP. LOT



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Dispense in tight,  
light-resistant container  
as defined in the USP  
with a child-resistant cap.

Store at 25°C (77°F). See  
USP Controlled Room  
Temperature; excursions  
permitted to 15° to 30°C  
(59° to 86°F).

Caution: Special Handling  
and Disposal instructions  
see insert.

Roxane Laboratories, Inc.  
Columbus, Ohio 43216

NDC 0054-0163-25 100 Capsules

**MYCOPHENOLATE  
MOFETIL  
Capsules**

**250 mg**

Each capsule contains 250 mg  
mycophenolate mofetil.

USUAL DOSAGE: For dosage  
recommendations and other  
important prescribing  
information, read  
accompanying insert.

R<sub>x</sub> only



Boehringer Ingelheim  
Roxane Laboratories

EXP. LOT



10004761/01  
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For the most current labeling information, please visit <https://www.fda.gov/drugs>

NDC 0054-0166-29

500 Tablets

**MYCOPHENOLATE  
MOFETIL  
Tablets**

**500 mg**

Each tablet contains 500 mg  
mycophenolate mofetil.

USUAL DOSAGE: For dosage  
recommendations and other  
important prescribing information,  
read accompanying insert.

R<sub>x</sub> only



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Roxane Laboratories

10004758/01  
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Caution: Special Handling and  
Disposal instructions see insert.



LOT  
EXP.

Dispense in tight, light-resistant  
container as defined in the USP with  
a child-resistant cap.

Store at 25°C (77°F). See USP  
Controlled Room Temperature;  
excursions permitted to 15° to 30°C  
(59° to 86°F).

Roxane Laboratories, Inc.  
Columbus, Ohio 43216

s label may not be the latest approved by FDA. For the latest prescribing information, please visit <https://www.fda.gov>

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Store at 25°C (77°F). See USP Controlled Room Temperature; excursions permitted to 15° to 30°C (59° to 86°F).

Caution: Special Handling and Disposal instructions see insert.

Roxane Laboratories, Inc.  
Columbus, Ohio 43216

NDC 0054-0166-25

100 Tablets

**MYCOPHENOLATE**  
**MOFETIL Tablets**  $\hat{E}$

**500 mg**

Each tablet contains 500 mg mycophenolate mol

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.  $\mathcal{R}_x$



Boehringer Ingelheim  
Roxane Laboratories

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