

Mycophenolate Mofetil Capsules, USP

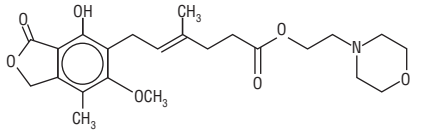
Mycophenolate Mofetil Tablets, USP

Rx Only

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS
Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning (see WARNINGS and PRECAUTIONS).
Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe mycophenolate. 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 (see WARNINGS and PRECAUTIONS).

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 an empirical formula of C₂₀H₂₈N₂O₈, a molecular weight of 433.50, and the following structural formula:



Mycophenolate mofetil, USP is a white to off-white crystalline powder. It is slightly soluble in water (43 µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.5). 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 (DSW), the pH of the reconstituted solution is 2.4 to 4.1. Mycophenolate mofetil is available for oral administration as capsules containing 250 mg of mycophenolate mofetil and tablets containing 500 mg of mycophenolate mofetil.

Inactive ingredients in Mycophenolate Mofetil Capsules USP, 250 mg include: croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain FD&C blue #2, gelatin, red iron oxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide and the printing ink contains shellac, propylene glycol, and black iron oxide.

Inactive ingredients in Mycophenolate Mofetil Tablets USP, 500 mg include: croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc, and titanium dioxide. Mycophenolate Mofetil Tablets USP, 500 mg comply with USP dissolution test 3.

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 arteriopathy 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 inhibition on DNA. Because 1- 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 the regulation of adhesion and may inhibit recruitment of leukocytes into sites of inflammation. Mycophenolate mofetil and its active metabolite, MPA, 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 systematically 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 µg/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 (271 g, 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_{max} was decreased by 40% in the presence of food (see DOSAGE AND ADMINISTRATION).

Distribution

The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following intravenous and oral administration, respectively. MPA, at clinically relevant concentrations, is 9% 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 to plasma proteins showed that salicylate (at 1 mg/mL), valproic acid (at 1 mg/mL), and HSA (at 1 mg/mL) did not displace MPA from its binding sites. At concentrations that exceed those seen in clinical practice, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tobramycin, and warfarin 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 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 pre-systemically 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*, MPAG is converted to MPA via enterhepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered 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 enterhepatic 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 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, the urine and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterhepatic recirculation of the drug (see OVERDOSEAGE).

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration and 16.6 (±5.8) hours and 177 (±37) mL/min following intravenous 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 posttransplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C_{max} approximately 32% to 44% lower compared to the healthy volunteers (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 followed by 1.5 g bid oral mycophenolate resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate 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 _{max} (h)	C _{max} (µg/mL)	Total AUC (µg·h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±17.2) (n=117)
Renal Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T _{max} (h)	C _{max} (µg/mL)	Interfering Interval AUC (0-12h) (µg·h/mL)
5 days	1 g/oral	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.63) (n=31)	32.9 (±15.0) (n=31)
Early (<40 days)	1 g/oral	1.31 (±0.75) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±5.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±33.7) (n=23)
Cardiac Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T _{max} (h)	C _{max} (µg/mL)	Interfering Interval AUC (0-12h) (µg·h/mL)
Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (>6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1 (±20.4) (n=49)
Hepatic Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T _{max} (h)	C _{max} (µg/mL)	Interfering Interval AUC (0-12h) (µg·h/mL)
4 to 9 days	1 g/iv	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (> 8 days)	1.5 g/oral	1.15 (±0.432) (n=6)	13.1 (±6.76) (n=6)	29.2 (±11.9) (n=6)
Late (>6 months)	1.5 g/oral	1.54 (±1.17) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

a 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 _{max} (h)	C _{max} (µg/mL)	AUC(0-96h) (µg·h/mL)
Healthy Volunteers (GFR >80 mL/min/1.73 m ² (n=6))	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment (GFR 50 to 80 mL/min/1.73 m ² (n=6))	1 g	0.75 (±0.27)	26.0 (±3.82)	59.9 (±25.9)
Moderate Renal Impairment (GFR 25 to 49 mL/min/1.73 m ² (n=6))	1 g	0.75 (±0.27)	19.0 (±8.12)	52.9 (±25.5)
Severe Renal Impairment (GFR <25 mL/min/1.73 m ² (n=7))	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Hepatic Impairment (no. of patients)	Dose	T _{max} (h)	C _{max} (µg/mL)	AUC(0-48h) (µg·h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic Cirrhosis (n=18)	1 g	0.85 (±0.58)	22.4 (±10.1)	25.8 (±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 m²) was about 73% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m²). In addition, the single-dose plasma MPA 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 m²) was 62.4 µg·h/mL (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see PRECAUTIONS: Patients with Renal Impairment 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: Patients with Renal Impairment 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 MPAG 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 µg/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 than 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 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 µg·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/m² 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 _{max} (h)	Dose Adjusted C _{max} (µg/mL)	Dose Adjusted AUC ₀₋₁₂ (µg·h/mL)
1 to <2 yr (6)	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to <6 yr (17)		1.13 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to <12 yr (21)		1.66 (3.90)	17.5 (14.9)	31.9 (19.6)
12 to 18 yr (11)		1.16 (0.830)	11.7 (10.7)	26.3 (9.14)
1 to <2 yr (4)	Late (Month 3)	0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to <6 yr (15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to <12 yr (14)		1.21 (0.532)	27.8 (21.1)	51.9 (19.6)
12 to 18 yr (17)		0.978 (0.484)	17.9 (9.57)	53.6 (20.3)
1 to <2 yr (4)	Late (Month 9)	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to <6 yr (12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to <12 yr (12)		1.02 (0.462)	28.2 (12.2)	55.8 (12.2)
12 to 18 yr (14)		1.09 (0.515)	18.1 (7.29)	56.7 (14.0)

a adjusted to a dose of 600 mg/m²

b n=20

c n=16

d a subset of 1 to <6 yr

The mycophenolate mofetil oral suspension dose of 600 mg/m² 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 posttransplant period. There was some 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 males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) µg·h/mL, while mean (±SD) MPA C_{max} was 9.6 (±4.9) in the males and 10.6 (±5.64) µg/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 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 azathioprine/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, and 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 transplant (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, when administered with antithymocyte globulin (ATGAM®) induction (with and without 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, 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 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 underestimates, 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 (n=159 patients)	Mycophenolate Mofetil 2 g/day (n=157 patients)	Mycophenolate Mofetil 3 g/day (n=166 patients)	Azathioprine 1 to 2 mg/kg/day (n=166 patients)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/Australia Study* (n=303 patients)	Mycophenolate Mofetil 2 g/day (n=172 patients)	Mycophenolate Mofetil 3 g/day (n=164 patients)	Azathioprine 10 to 150 mg/day (n=166 patients)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study† (n=491 patients)	Mycophenolate Mofetil 2 g/day (n=165 patients)	Mycophenolate Mofetil 3 g/day (n=160 patients)	Placebo (n=166 patients)
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

a Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.

b Doses include azathioprine and graft loss as reason for early termination.

c MMF or azathioprine/cyclosporine/corticosteroids.

d MMF or placebo/cyclosporine/corticosteroids.

The cumulative incidence of 12-month graft loss or patient death is presented below. No advantage of mycophenolate 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%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Pediatrics

One open-label, safety and pharmacokinetic study of mycophenolate mofetil oral suspension 600 mg/m² 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 pharmacokinetic 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 <5 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 were received study drug and 578 received study drug. Patients received mycophenolate mofetil 1.5 g bid or azathioprine 1.5 to 3 mg/kg/day (n=288), 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 following transplantation; and (2) the proportion of patients who prematurely discontinued treatment during the first 12 months posttransplant. 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

practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the healthcare community better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected 1995 to 2007) on 77 fetuses exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4% to 5% among babies born to organ transplant patients using other immunosuppressive drugs.

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil (MMF) doses equivalent to 0.02 to 0.9 times the recommended human dose for renal and cardiac transplant patients, based on body surface area conversions. In rat offspring, malformations included anophthalmia, agnathia, and hydrocephaly. In rabbit offspring, malformations included ectopic cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia.

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 from pediatric patients after renal transplantation, the recommended dose of Mycophenolate Mofetil oral suspension is 600 mg/m² 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 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 include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections e.g., opportunistic (see **WARNINGS: Serious Infections** and **WARNINGS: New or Reactivated Viral Infections**). The adverse event profile associated with the administration of Mycophenolate Mofetil Intravenous has been shown to be similar to that observed after administration of oral dosage forms of mycophenolate.

Mycophenolate Oral

The incidence of adverse events for mycophenolate 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 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 treatment groups are presented below.

Table 9 Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in >20% of Patients in the Mycophenolate Group)

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate Mofetil 2 g/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Body as a Whole							
Pain	33.0	31.2	32.2	75.8	74.7	74.0	77.7
Abdominal pain	24.7	27.6	23.0	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	26.0	—	—
Back pain	—	—	—	34.6	28.4	46.6	47.4
Ascites	—	—	—	—	—	24.2	22.6
Hematologic and Lymphatic							
Anemia	25.6	25.8	23.6	42.9	43.9	43.0	53.0
Leukopenia	23.2	34.5	24.8	30.4	38.1	45.8	38.0
Thrombocytopenia	—	—	—	23.5	27.0	38.3	42.2
Hypochromic anemia	—	—	—	24.6	23.5	—	—
Leukopenia	—	—	—	40.5	35.6	22.4	21.3
Urogenital							
Urinary tract infection	37.2	37.0	33.7	—	—	—	—
Kidney function abnormal	—	—	—	21.8	26.3	25.6	28.9
Cardiovascular							
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6
Hypotension	—	—	—	32.5	36.0	—	—
Cardiovascular disorder	—	—	—	25.6	24.2	—	—
Tachycardia	—	—	—	20.1	18.0	22.0	15.7
Metabolic and Nutritional							
Peripheral edema	28.6	27.0	28.2	64.0	53.3	48.4	47.7
Hypochloremia	—	—	—	41.2	38.4	—	—
Edema	—	—	—	26.6	25.6	28.2	28.2
Hypokalemia	—	—	—	31.8	25.6	37.2	41.1
Hypomagnesemia	—	—	—	—	—	22.0	23.7
Hyperglycemia	—	—	—	46.7	52.6	43.7	48.8
Creatinine increased	—	—	—	39.4	36.0	—	—
BUN increased	—	—	—	34.6	32.5	—	—
Lactic dehydrogenase increased	—	—	—	23.2	17.0	—	—
Hypomagnesemia	—	—	—	—	—	39.0	37.6
Hypocalcemia	—	—	—	—	—	30.0	30.0
Digestive							
Diarrhea	31.0	36.1	20.8	45.3	34.3	51.3	49.8
Constipation	22.9	19.5	22.4	41.2	37.7	37.9	38.3
Nausea	19.9	23.6	24.5	54.0	54.3	54.5	51.2
Dyspepsia	—	—	—	—	22.4	20.9	20.9
Vomiting	—	—	—	33.9	28.4	32.9	33.4
Anorexia	—	—	—	—	—	25.3	17.1
Liver function tests abnormal	—	—	—	—	—	24.9	19.2
Respiratory							
Infection	22.0	23.9	19.6	37.0	35.3	—	—
Dyspnea	—	—	—	36.7	36.3	31.0	30.3
Cough increased	—	—	—	31.1	25.6	—	—
Lung disorder	—	—	—	30.1	29.1	22.0	18.8
Sinusitis	—	—	—	26.0	19.0	—	—
Pleural effusion	—	—	—	—	—	34.3	35.9
Skin and Appendages							
Rash	—	—	—	22.1	18.0	—	—
Nervous System							
Tremor	—	—	—	24.2	23.9	33.9	35.5
Insomnia	—	—	—	40.8	37.7	52.3	47.0
Dizziness	—	—	—	28.7	27.7	—	—
Anxiety	—	—	—	28.4	23.9	—	—
Paresthesia	—	—	—	20.8	18.0	—	—

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 compared to patients treated with azathioprine. The incidence of sepsis was comparable in mycophenolate 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 compared to patients receiving azathioprine, but was comparable in hepatic transplant patients treated with mycophenolate or azathioprine.

Patients receiving mycophenolate 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 (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 × 10⁹/L) developed in up to 2.0% 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: Serious Infections and WARNINGS: New or Reactivated Viral Infections**). Table 10 shows the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials:

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate Mofetil 2 g/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	Mycophenolate Mofetil 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Herpes simplex	16.7	20.0	19.0	20.8	14.5	10.1	5.9
CMV	—	—	—	—	—	—	—
— Viremia/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	17.6	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 patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease, Candida, urinary tract infection, fungemia/disseminated disease, tissue invasive disease, Cryptococcus, 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 studies, with a notably lower incidence of the following: Herpes simplex and CMV tissue-invasive disease.

In patients receiving mycophenolate mofetil (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **WARNINGS: Serious Infections**). In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with mycophenolate than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with mycophenolate.

The following adverse events were reported with 3% to <20% incidence in renal, cardiac, and hepatic transplant patients treated with mycophenolate, in combination with cyclosporine and corticosteroids.

Table 11 Adverse Events Reported in 3% to <20% of Patients Treated With Mycophenolate in Combination With Cyclosporine and Corticosteroids

Body System	
Body as a Whole	abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis
Hematologic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased
Urogenital	acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis, nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder
Cardiovascular	angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased
Metabolic and Nutritional	abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesterolemia, hyperlipidemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss
Digestive	anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis
Respiratory	apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration
Skin and Appendages	acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash
Nervous	agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertension, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo
Endocrine	Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder
Musculoskeletal	arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis
Special Senses	abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder

Pediatrics

The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with Mycophenolate Mofetil oral suspension 600 mg/m² bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with Mycophenolate Mofetil Capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, leukopenia, and anemia, which were observed in a higher proportion in pediatric patients.

Postmarketing Experience

Concurrent Disorders: Overdose of mycophenolate in humans is very limited. The events received from reports of overdose fall within the known safety profile of the drug. The highest doses administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Hematologic and Lymphatic: Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with mycophenolate in combination with other immunosuppressive agents.

Infections (see **WARNINGS: Serious Infections, New or Reactivated Viral Infections):**

- Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally.
- There is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.
- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate. The reported cases generally had risk factors for PML, including treatment with immunosuppressive therapies and impairment of immune function.
- Polyomavirus associated neuropathy (PVAN), especially due to BK virus infection, has been observed in patients receiving immunosuppressants, including mycophenolate. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss.
- Viral reactivation has been reported in patients infected with HBV or HCV.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving mycophenolate.

OVERDOSEAGE

The experience with overdose of mycophenolate in humans is very limited. The events received from reports of overdose fall within the known safety profile of the drug. The highest doses administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 1000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients and approximately 7 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In adult rats, deaths occurred after single oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents approximately 3 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

DOSAGE AND ADMINISTRATION

Renal Transplantation

A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of mycophenolate mofetil demonstrated an overall better safety profile than did patients receiving 3 g/day of mycophenolate mofetil.

Pediatrics (3 months to 18 years of age)

The recommended dose of Mycophenolate Mofetil oral suspension is 600 mg/m² administered twice daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body surface area of 1.25 m² to 1.5 m² may be dosed with Mycophenolate Mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 m² may be dosed with Mycophenolate Mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

Cardiac Transplantation

Adults

A dose of 1.5 g bid (daily dose of 3 g) is recommended for use in adult cardiac transplant patients.

Hepatic Transplantation

Adults

A dose of 1.5 g bid (daily dose of 3 g) is recommended for use in adult hepatic transplant patients.

Mycophenolate Mofetil Capsules, Tablets, and Oral Suspension

The initial oral dose of mycophenolate should be given as soon as possible following renal, cardiac or hepatic transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. Therefore, it is recommended that mycophenolate be administered on an empty stomach. However, in stable renal transplant patients, mycophenolate may be administered with food if necessary. Patients should be instructed to take a missed dose as soon as they remember, except if it is near the next scheduled dose, and then continue to take mycophenolate at the usual times.

Note:

If required, Mycophenolate Mofetil Oral Suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Patients With Hepatic Impairment

No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

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

Geriatrics

The recommended oral dose of 1 g bid for renal transplant patients, 1.5 g bid for cardiac transplant patients, and 1.5 g bid administered orally in hepatic transplant patients is appropriate for elderly patients (see **PRECAUTIONS: Geriatric Use**).