Between text matter to 2D Code the blank space should be min. 5mm.

Do not print pink colour line.

- Space for 15 Digit Sequential 2D Data matrix Barcode shall be printed by the vendor.
- 2D data matrix should be minimum 8mm to 10mm height & width.
- 2D data matrix should be printed in the middle of the blank space in the folded Outsert.

Pharma code should be at least 8mm height after folding the Outserts, this is minimum required height to read on line during packing.

Position / Orientation shall be changed depending upon the Printer's Machine suitability.

Mycophenolate Mofetil
Mycophenolate Sodium
Capsules USP 360 mg

1052748

PDC

Mycophenolate Mofetil
Mycophenolate Sodium
Capsules USP 180 mg

1052748

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYCOPHENOLATE MOFETIL CAPSULES and MYCOPHENOLATE MOFETIL TABLETS safely and effectively. See full prescribing information for MYCOPHENOLATE MOFETIL CAPSULES and MYCOPHENOLATE MOFETIL TABLETS.

MYCOPHENOLATE MOFETIL capsules, for oral use
MYCOPHENOLATE MOFETIL tablets, for oral use

Initial U.S. Approval: 1995

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES and SERIOUS INFECTIONS
See full prescribing information for complete boxed warning
- **Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning *(see Warnings and Precautions (5.1))*.**
- **Increased risk of development of lymphoma and other malignancies, particularly of the skin *(see Warnings and Precautions (5.2))*.**
- **Increased susceptibility to infections, including opportunistic infections and severe infections with fatal outcomes *(see Warnings and Precautions (5.3))*.**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.8) ----------08/2025

----------INDICATIONS AND USAGE----------
Mycophenolate mofetil is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. (1)

----------DOSAGE AND ADMINISTRATION----------

ADULTS	DOSAGE
Kidney Transplant	1 g twice daily, orally (2.2)
Heart Transplant	1.5 g twice daily, orally (2.3)
Liver Transplant	1.5 g twice daily orally (2.4)
PEDIATRICS	
Kidney Transplant	600 mg/m² orally twice daily, up to maximum of 2 g daily (2.2)
Heart Transplant	600 mg/m² orally twice daily (starting dose) up to a maximum of 900 mg/m² twice daily (2.3)
Liver Transplant	600 mg/m² orally twice daily (starting dose) up to a maximum of 900 mg/m² twice daily (2.4)

- Reduce or interrupt dosing in the event of neutropenia. (2.5)
- See full prescribing information (FPI) for: adjustments for renal impairment and neutropenia (2.5).

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES and SERIOUS INFECTIONS
- **Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning *(see Warnings and Precautions (5.1), Use in Special Populations (8.1, 8.3))*.**
- **Increased risk of development of lymphoma and other malignancies, particularly of the skin *(see Warnings and Precautions (5.2))*.**
- **Increased susceptibility to bacterial, viral, fungal and protozoal infections, including opportunistic infections and viral reactivation of hepatitis B and C, which may lead to hospitalizations and fatal outcomes *(see Warnings and Precautions (5.3))*.**

1 INDICATIONS AND USAGE
Mycophenolate mofetil (MMF) is indicated for the prophylaxis of organ rejection, in adult and pediatric recipients 3 months of age and older of allogeneic kidney *(see Clinical Studies (14.1))*, heart *(see Clinical Studies (14.2))* or liver transplants *(see Clinical Studies (14.3))*, in combination with other immunosuppressants.

2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
Mycophenolate mofetil should not be used without the supervision of a physician with experience in immunosuppressive therapy.

Mycophenolate Mofetil Capsules and Tablets
Mycophenolate mofetil oral dosage forms (capsules or tablets) **should not be used interchangeably with mycophenolic acid delayed-release tablets without supervision of a physician with experience in immunosuppressive therapy** because the rates of absorption following the administration of mycophenolate mofetil oral dosage forms and mycophenolic acid delayed-release tablets are not equivalent.

Mycophenolate mofetil tablets should not be crushed and mycophenolate mofetil capsules should not be opened or crushed. Patients should avoid inhalation or contact of the skin or mucous membranes with the powder contained in mycophenolate mofetil capsules. If such contact occurs, they must wash the area of contact thoroughly with soap and water. In case of ocular contact, rinse eyes with plain water.

The initial oral dose of mycophenolate mofetil should be given as soon as possible following kidney, heart or liver transplant. It is recommended that mycophenolate mofetil be administered on an empty stomach. In stable transplant patients, however, mycophenolate mofetil may be administered with food if necessary *(see Clinical Pharmacology (12.3))*.
Patients should be instructed to take a missed dose as soon as they remember, except if it is closer than 2 hours to the next scheduled dose; in this case, they should continue to take mycophenolate mofetil at the usual times.

2.2 Dosage Recommendations for Kidney Transplant Patients
Adults
The recommended dosage for adult kidney transplant patients is 1 g orally, twice daily (total daily dose of 2 g).

Pediatrics (3 months and older)
Pediatric dosing is based on body surface area (BSA). The recommended dosage of mycophenolate mofetil for oral suspension for pediatric kidney transplant patients 3 months and older is 600 mg/m², administered twice daily (maximum total daily dose of 2 g or 10 mL of the oral suspension). Pediatric patients with BSA ≥1.25 m² may be dosed with capsules or tablets as follows:

Table 1 Pediatric Kidney Transplant: Dosage Using Capsules or Tablets

Body Surface Area	Dosage
1.25 m² to <1.5 m²	Mycophenolate mofetil capsule 750 mg twice daily (1.5 g total daily dose)
≥ 1.5 m²	Mycophenolate mofetil capsules or tablets 1 g twice daily (2 g total daily dose)

2.3 Dosage Recommendations for Heart Transplant Patients
Adults
The recommended dosage of Mycophenolate mofetil for adult heart transplant patients is 1.5 g orally administered twice daily (total daily dose of 3 g).

Pediatrics (3 months and older)
The recommended starting dosage of Mycophenolate mofetil oral suspension for pediatric heart transplant patients 3 months and older is 600 mg/m², administered twice daily. If well tolerated, the dose can be increased to a maintenance dosage of 900 mg/m² twice daily (maximum total daily dose of 3 g or 15 mL of the oral suspension). The dose may be individualized based on clinical assessment.

Pediatric patients with BSA ≥1.25 m² may be started on therapy with capsules or tablets as follows:

Table 2 Pediatric Heart Transplant: Pediatric Starting Dosage Using Capsules or Tablets

Body Surface Area	Starting Dosage*
1.25 m² to <1.5 m²	Mycophenolate mofetil capsule 750 mg twice daily (1.5 g total daily dose)
≥ 1.5 m²	Mycophenolate mofetil capsules or tablets 1 g twice daily (2 g total daily dose)

*Maximum maintenance dose: 3 g total daily.

2.4 Dosage Recommendations for Liver Transplant Patients
Adults
The recommended dosage of Mycophenolate mofetil for adult liver transplant patients is 1.5 g administered orally twice daily (total daily dose of 3 g).

Pediatrics (3 months and older)
The recommended starting dosage of Mycophenolate mofetil oral suspension for pediatric liver transplant patients 3 months of age and older is 600 mg/m², administered twice daily. If well tolerated, the dose can be increased to a maintenance dosage of 900 mg/m² twice daily (maximum total daily dose of 3 g or 15 mL of the oral suspension). The dose may be individualized based on clinical assessment.

Pediatric patients with BSA ≥1.25 m² may be started on therapy with capsules or tablets as follows:

Table 3 Pediatric Liver Transplant: Pediatric Starting Dosage Using Capsules or Tablets

Body Surface Area	Starting Dosage*
1.25 m² to <1.5 m²	Mycophenolate mofetil capsule 750 mg twice daily (1.5 g total daily dose)
≥ 1.5 m²	Mycophenolate mofetil capsules or tablets 1 g twice daily (2 g total daily dose)

*Maximum maintenance dose: 3 g total daily.

2.5 Dosage Modifications: Patients with Renal Impairment, Neutropenia
Renal Impairment
No dosage modifications are needed in kidney transplant patients with delayed graft function postoperatively *(see Clinical Pharmacology (12.3))*. In kidney transplant patients with severe chronic impairment of the graft (GFR <25 mL/min/1.73 m²), do not administer doses of mycophenolate mofetil greater than 1 g twice a day. These patients should be carefully monitored *(see Clinical Pharmacology (12.3))*.

Neutropenia
If neutropenia develops (ANC <1.3 x 10³/µL), dosing with mycophenolate mofetil should be interrupted or reduced, appropriate diagnostic tests performed, and the patient managed appropriately *(see Warnings and Precautions (5.4) and Adverse Reactions (6.1))*.

3 DOSAGE FORMS AND STRENGTHS
Mycophenolate mofetil for tablets and capsules are available in the following dosage forms and strengths:

Capsules	250 mg mycophenolate mofetil, white to off-white blend of mycophenolate mofetil filled in size "1" hard gelatin capsule with Ivory Cap and Ivory Body, printed "SAL" on cap and "726" on body in black.
Tablets	500 mg mycophenolate mofetil, pinkish brown colored, capsule shaped, film coated tablet with "SAL" engraved on one side and engraved "725" on other side.

4 CONTRAINDICATIONS
Mycophenolate Mofetil is contraindicated in patients with a history of hypersensitivity, including anaphylaxis, to mycophenolate mofetil (MMF), mycophenolic acid (MPA) or any component of the drug product *(see Warning and Precautions (5.8))*.

5 WARNINGS AND PRECAUTIONS
5.1 Embryofetal Toxicity
Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney and nervous system. Females of reproductive potential must be made aware of these risks and must be counseled regarding pregnancy prevention and planning. Avoid use of MMF during pregnancy if safer treatment options are available *(see Use in Specific Populations (8.1, 8.3))*.

5.2 Lymphoma and Other Malignancies
Patients receiving immunosuppressants, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin *(see Adverse Reactions (6.1))*. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. For patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD) developed in 0.4% to 1% of patients receiving mycophenolate mofetil (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of kidney, heart and liver transplant patients *(see Adverse Reactions (6.1))*. The majority of PTLD cases appear to be related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children. In pediatric patients, no other malignancies besides PTLD were observed in clinical trials *(see Adverse Reactions (6.1))*.

5.3 Serious Infections
Patients receiving immunosuppressants, including mycophenolate mofetil, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. The risk increases with the total immunosuppressive load. These infections may lead to serious outcomes, including hospitalizations and death *(see Adverse Reactions (6.1, 6.2))*.
Serious viral infections reported include:
- Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infection
- JC virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.
- Viral reactivation in patients infected with Hepatitis B and C
- COVID-19

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 250 mg
- Tablets: 500 mg

----------CONTRAINDICATIONS----------
- History of hypersensitivity, including anaphylaxis, to mycophenolate mofetil, mycophenolic acid or any component of the drug product (4)

----------WARNINGS AND PRECAUTIONS----------
- Blood Dyscrasias (Neutropenia, Red Blood Cell Aplasia): Monitor with blood tests; consider treatment interruption or dose reduction. (5.4)
- Gastrointestinal Complications: Monitor for complications such as bleeding, ulceration and perforations, particularly in patients with underlying gastrointestinal disorders. (5.5)
- Hypoxanthine-Guanine Phosphoribosyl-Transferase Deficiency: Avoid use of mycophenolate mofetil. (5.6)
- Acute Inflammatory Syndrome Associated with Mycophenolate Products: Monitor for this paradoxical inflammatory reaction. (5.7)
- Hypersensitivity Reactions: Discontinue mycophenolate mofetil; treat and monitor until signs and symptoms resolve (5.8)
- Immunizations: Avoid live attenuated vaccines. (5.9)
- Blood Donation: Avoid during therapy and for 6 weeks thereafter. (5.12)
- Semen Donation: Avoid during therapy and for 90 days thereafter. (5.13)
- Potential Impairment on Driving and Use of Machinery: Mycophenolate Mofetil may affect ability to drive or operate machinery. (5.15)

----------ADVERSE REACTIONS----------
The most common adverse reactions in clinical trials (20 % or greater) include diarrhea, leukopenia, infection, vomiting, and there is evidence of a higher frequency of certain types of infections e.g., opportunistic infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.com

----------DRUG INTERACTIONS----------
- See FPI for drugs that may interfere with systemic exposure and reduce mycophenolate mofetil efficacy: antacids with magnesium or aluminum hydroxide, proton pump inhibitors, drugs that interfere with enterohepatic recirculation, telmisartan, calcium-free phosphate binders. (7.1)
- Mycophenolate mofetil may reduce effectiveness of oral contraceptives. Use of additional barrier contraceptive methods is recommended. (7.2)
- See FPI for other important drug interactions. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Male Patients: Sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2025

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*Sections or subsections omitted from the full prescribing information are not listed.

Consider dose reduction or discontinuation of mycophenolate mofetil in patients who develop new infections or reactivate viral infections, weighing the risk that reduced immunosuppression represents to the functioning allograft.
PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss *(see Adverse Reactions (6.2))*. Patient monitoring may help detect patients at risk for PVAN.
PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia *(see Adverse Reactions (6.2))*. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms.
The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease.
Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

5.4 Blood Dyscrasias: Neutropenia and Pure Red Cell Aplasia (PRCA)
Severe neutropenia (absolute neutrophil count (ANC) <0.5 x 10³/µL) developed in transplant patients receiving mycophenolate mofetil 3 g daily *(see Adverse Reactions (6.1))*. Patients receiving mycophenolate mofetil should be monitored for neutropenia. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of kidney, heart and liver rejection. The development of neutropenia may be related to mycophenolate mofetil itself, concomitant medications, viral infections, or a combination of these causes. If neutropenia develops (ANC <1.3 x 10³/µL), dosing with mycophenolate mofetil should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately *(see Dosage and Administration (2.5))*.

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

Consider monitoring with complete blood counts weekly for the first month, twice monthly for the second and third months, and monthly for the remainder of the first year.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of mycophenolate mofetil therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

5.5 Gastrointestinal Complications
Gastrointestinal bleeding requiring hospitalization, ulceration and perforations were observed in clinical trials. Physicians should be aware of these serious adverse effects particularly when administering mycophenolate mofetil to patients with a gastrointestinal disease.

5.6 Patients with Hypoxanthine-Guanine Phosphoribosyl-Transferase Deficiency (HGPRT)
Mycophenolate mofetil is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; therefore it should be avoided in patients with hereditary deficiencies of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.

5.7 Acute Inflammatory Syndrome Associated with Mycophenolate Products
Acute inflammatory syndrome (AIS) has been reported with the use of MMF and mycophenolate products, and some cases have resulted in hospitalization. AIS is a paradoxical pro-inflammatory response characterized by fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers including, C-reactive protein and erythrocyte sedimentation rate, without evidence of infection or underlying disease recurrence. Symptoms occur within weeks to months of initiation of treatment or a dose increase. After discontinuation, improvement of symptoms and inflammatory markers are usually observed within 24 to 48 hours.

Monitor patients for symptoms and laboratory parameters of AIS when starting treatment with mycophenolate products or when increasing the dosage. Discontinue treatment and consider other treatment alternatives based on the risk and benefit for the patient.

5.8 Hypersensitivity Reactions
Postmarketing cases of hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with mycophenolate mofetil. These reactions generally occurred within hours to the next day after initiating mycophenolate mofetil. If signs or symptoms of hypersensitivity reaction occur, discontinue mycophenolate mofetil; treat and monitor until symptoms resolve *[see Contraindications (4)]*.

5.9 Immunizations
During treatment with mycophenolate mofetil, the use of live attenuated vaccines should be avoided (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) and patients should be advised that vaccinations may be less effective. Advise patients to discuss with the physician before seeking any immunizations.

5.12 Blood Donation
Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of mycophenolate mofetil because their blood or blood products might be administered to a female of reproductive potential or a pregnant woman.

5.13 Semen Donation
Based on animal data, men should not donate semen during therapy and for 90 days following discontinuation of mycophenolate mofetil *(see Use In Specific Populations (8.3))*.

5.14 Effect of Concomitant Medications on Mycophenolic Acid Concentrations
A variety of drugs have potential to alter systemic MPA exposure when co-administered with mycophenolate mofetil. Therefore, determination of MPA concentrations in plasma before and after making any changes to immunosuppressive therapy, or when adding or discontinuing concomitant medications, may be appropriate to ensure MPA concentrations remain stable.

5.15 Potential Impairment of Ability to Drive or Operate Machinery
Mycophenolate mofetil may impact the ability to drive and use machines. Patients should avoid driving or using machines if they experience somnolence, confusion, dizziness, tremor, or hypotension during treatment with mycophenolate mofetil *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Embryofetal Toxicity *[see Warnings and Precautions (5.1)]*
- Lymphomas and Other Malignancies *[see Warnings and Precautions (5.2)]*
- Serious Infections *[see Warnings and Precautions (5.3)]*
- Blood Dyscrasias: Neutropenia, Pure Red Cell Aplasia *[see Warnings and Precautions (5.4)]*
- Gastrointestinal Complications *[see Warnings and Precautions (5.5)]*
- Acute Inflammatory Syndrome Associated with Mycophenolate Products *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
An estimated total of 1557 adult patients received mycophenolate mofetil during pivotal clinical trials in the prevention of acute organ rejection. Of these, 991 were included in the three renal studies, 277 were included in one hepatic study, and 289 were included in one cardiac study. Patients in all study arms also received cyclosporine and corticosteroids.

The data described below primarily derive from five randomized, active-controlled double-blind 12-month trials of mycophenolate mofetil in *de novo* kidney (3) heart (1) and liver (1) transplant patients *[see Clinical Studies (14.1, 14.2, and 14.3)]*.

Mycophenolate Mofetil Oral
The incidence of adverse reactions for mycophenolate mofetil was determined in five randomized, comparative, double-blind trials in the prevention of rejection in kidney, heart and liver transplant patients (two active- and one placebo-controlled trials, one active-controlled trial, and one active-controlled trial, respectively) *[see Clinical Studies (14.1, 14.2 and 14.3)]*.
The three *de novo* kidney studies with 12-month duration compared two dose levels of oral mycophenolate mofetil (1 g twice daily and 1.5 g twice daily) 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 anti-thymocyte globulin (ATGAM®) induction therapy.

In the *de novo* heart transplantation study with 12-month duration, patients received mycophenolate mofetil 1.5 g twice daily (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.

In the *de novo* liver transplantation study with 12-month duration, patients received mycophenolate mofetil 1 g twice daily intravenously for up to 14 days followed by mycophenolate mofetil 1.5 g twice daily orally or azathioprine 1 to 2 mg/kg/day intravenously followed by azathioprine 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The total number of patients enrolled was 565.

Approximately 53% of the kidney transplant patients, 65% of the heart transplant patients, and 48% of the liver transplant patients were treated for more than 1 year. Adverse reactions reported in ≥20% of patients in the mycophenolate mofetil treatment groups are presented below. The safety data of three kidney transplantation studies are pooled together.

Table 5 Adverse Reactions in Controlled Studies of De Novo Kidney, Heart or Liver Transplantation Reported in ≥20% of Patients in the Mycophenolate Mofetil Group

Adverse drug reaction	Kidney Studies			Heart Study		Liver Study	
System Organ Class	Mycophenolate mofetil 2g/day (n=501) or 3g/day (n=490)	AZA 1 to 2 mg/kg/day or 100 to 150 mg/day	Placebo	Mycophenolate mofetil 3g/day	AZA 1.5 to 3 mg/kg/day	Mycophenolate Mofetil 3g/day	AZA 1 to 2 mg/kg/day
	(n=991)	(n=326)	(n=166)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Infections and infestations							
Bacterial infections	39.9	33.7	37.3	-	-	27.4	26.5
Viral infections	-*	-	-	31.1	24.9	-	-
Blood and lymphatic system disorders							
Anemia	20.0	23.6	2.4	45.0	47.1	43.0	53.0
Ecchymosis	-	-	-	20.1	9.7	-	-
Leukocytosis	-	-	-	42.6	37.4	22.4	21.3
Leukopenia	28.6	24.8	4.2	34.3	43.3	45.8	39.0
Thrombocytopenia	-	-	-	24.2	28.0	38.3	42.2
Metabolism and nutrition disorders							
Hypercholesterolemia	-	-	-	46.0	43.9	-	-
Hyperglycemia	-	-	-	48.4	53.3	43.7	48.8
Hyperkalemia	-	-	-	-	-	22.0	23.7
Hypocalcemia	-	-	-	-	-	30.0	30.0
Hypokalemia	-	-	-	32.5	26.3	37.2	41.1
Hypomagnesemia	-	-	-	20.1	14.2	39.0	37.6
Psychiatric disorders							
Depression	-	-	-	20.1	15.2	-	-
Insomnia	-	-	-	43.3	39.8	52.3	47.0
Nervous system disorders							
Dizziness	-	-	-	34.3	33.9	-	-
Headache	-	-	-	58.5	55.4	53.8	49.1
Tremor	-	-	-	26.3	25.6	33.9	35.5
Cardiac disorders							
Tachycardia	-	-	-	22.8	21.8	22.0	15.7
Vascular disorders							
Hypertension	27.5	32.2	19.3	78.9	74.0	62.1	59.6
Hypotension	-	-	-	34.3	40.1	-	-
Respiratory, thoracic and mediastinal disorders							
Cough	-	-	-	40.5	32.2	-	-
Dyspnea	-	-	-	44.3	44.3	31.0	30.3
Pleural effusion	-	-	-	-	-	34.3	35.9
Gastrointestinal disorders							
Abdominal pain	22.4	23.0	11.4	41.9	39.4	62.5	51.2
Constipation	-	-	-	43.6	38.8	37.9	38.3
Decreased appetite	-	-	-	-	-	25.3	17.1
Diarrhea	30.4	20.9	13.9	52.6	39.4	51.3	49.8
Dyspepsia	-	-	-	22.1	22.1	22.4	20.9
Nausea	-	-	-	56.1	60.2	54.5	51.2
Vomiting	-	-	-	39.1	34.6	32.9	33.4
Hepatobiliary disorders							
Blood lactate dehydrogenase increased	-	-	-	23.5	18.3	-	-
Hepatic enzyme increased	-	-	-	-	-	24.9	19.2
Skin and subcutaneous tissues disorders							
Rash	-	-	-	26.0	20.8	-	-
Renal and urinary disorders							
Blood creatinine increased	-	-	-	42.2	39.8	-	-
Blood urea increased	-	-	-	36.7	34.3	-	-
General disorders and administration site conditions							
Asthenia	-	-	-	49.1	41.2	35.4	33.8
Edema [a]	21.0	28.2	8.4	67.5	55.7	48.4	47.7
Pain [t]	24.8	32.2	9.6	79.2	77.5	74.0	77.5
Pyrexia	-	-	-	56.4	53.6	52.3	56.1

*: "-" Indicates that the incidence was below the cutoff value of 20% for inclusion in the table.
[a]: "Edema" includes peripheral edema, facial edema, scrotal edema.
[t]: "Pain" includes musculoskeletal pain (myalgia, neck pain, back pain).

In the three *de novo* kidney studies, patients receiving 2 g/day of mycophenolate mofetil had an overall better safety profile than did patients receiving 3 g/day of mycophenolate mofetil.

Post-transplant lymphoproliferative disease (PTLD, pseudolymphoma) 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 kidney, heart and liver transplant patients followed for at least 1 year *[see Warnings and Precautions (5.2)]*. 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 kidney and heart transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. In pediatric patients, PTLD was observed in 1.35% (2/148) by 12 months post-transplant.

Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia are a known risk associated with mycophenolate and may lead or contribute to the occurrence of infections and hemorrhages *[see Warnings and Precautions (5.3)]*. Severe neutropenia (ANC <0.5 x 10³/µL) developed in up to 2% of kidney transplant patients, up to 2.8% of heart transplant patients and up to 3.6% of liver transplant patients receiving mycophenolate mofetil 3 g daily *[see Warnings and Precautions (5.4) and Dosage and Administration (2.5)]*.

The most common opportunistic infections in patients receiving mycophenolate mofetil with other immunosuppressants were mucocutaneous candida, CMV viremia/syndrome, and herpes simplex. The proportion of patients with CMV viremia/syndrome was 13.5%. In patients receiving mycophenolate mofetil (2 g or 3 g) in controlled studies for prevention of kidney, heart or liver rejection, fatal infection/sepsis occurred in approximately 2% of kidney and heart patients and in 5% of liver patients *[see Warnings and Precautions (5.3)]*.

The most serious gastrointestinal disorders reported were ulceration and hemorrhage, which are known risks associated with mycophenolate mofetil. Mouth, esophageal, gastric, duodenal, and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials, while the most common gastrointestinal disorders were diarrhea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhea revealed isolated cases of intestinal villous atrophy *[see Warnings and Precautions (5.5)]*.

The following adverse reactions were reported with 3% to <20% incidence in kidney, heart, and liver transplant patients treated with mycophenolate mofetil, in combination with cyclosporine and corticosteroids.

Table 6 Adverse Reactions in Controlled Studies of De Novo Kidney, Heart or Liver Transplantation Reported in 3% to <20% of Patients Treated with Mycophenolate Mofetil in Combination with Cyclosporine and Corticosteroids

System Organ Class	Adverse Reactions
Body as a Whole	cellulitis, chills, hernia, malaise
Infections and Infestations	fungal infections
Hematologic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia
Urogenital	hematuria
Cardiovascular	hypotension
Metabolic and Nutritional	acidosis, alkaline phosphatase increased, hyperlipemia, hypophosphatemia, weight loss
Digestive	esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, hepatitis, ileus, nausea and vomiting, stomach ulcer, stomatitis
Neoplasm benign, malignant and unspecified	neoplasm
Skin and Appendages	skin benign neoplasm, skin carcinoma
Psychiatric	confusional state
Nervous	hypertonia, paresthesia, somnolence
Musculoskeletal	arthralgia, myasthenia

Pediatrics
The type and frequency of adverse events in a clinical study for prevention of kidney allograft rejection in 100 pediatric patients 3 months to 18 years of age dosed with mycophenolate mofetil oral suspension 600 mg/m² twice daily (up to 1 g twice daily) were generally similar to those observed in adult patients dosed with mycophenolate mofetil capsules at a dose of 1 g twice daily 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.

Safety information in pediatric heart transplant or pediatric liver transplant patients treated with mycophenolate mofetil is supported by an open-label study in pediatric liver transplant patients and publications; the type and frequency of the reported adverse reactions are consistent with those observed in pediatric patients following renal transplant and in adults.

Geriatrics
Geriatric 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 Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

and take your next dose at your normal scheduled time. **Do not** take 2 doses at the same time. Call your doctor if you are not sure what to do.

- Take mycophenolate mofetil capsules and tablets on an empty stomach, unless your doctor tells you otherwise. **Do not** crush mycophenolate mofetil tablets.
- **Do not** open or crush mycophenolate mofetil capsules.
- If you are not able to swallow mycophenolate mofetil tablets or capsules, your doctor may prescribe mycophenolate mofetil oral suspension. This is a liquid form of mycophenolate mofetil. Your pharmacist will mix the medicine before you pick it up from a pharmacy.
- **Do not** breathe in (inhale) or let mycophenolate mofetil powder or oral suspension come in contact with your skin or mucous membranes.
  - If you accidentally get the powder or oral suspension on the skin, wash the area well with soap and water.
  - If you accidentally get the powder or oral suspension in your eyes or other mucous membranes, flush with plain water.
- If you take too much mycophenolate mofetil, call your doctor or the poison control center right away.

What should I avoid while taking mycophenolate mofetil?

- Avoid becoming pregnant. (See **"What is the most important information I should know about mycophenolate mofetil?"**).
- Limit the amount of time you spend in sunlight. Avoid using tanning beds or sunlamps. People who take mycophenolate mofetil have a higher risk of getting skin cancer (See **"What is the most important information I should know about mycophenolate mofetil?"**). Wear protective clothing when you are in the sun and use a broad-spectrum sunscreen with a high protection factor. This is especially important if your skin is very fair or if you have a family history of skin cancer.
- You should not donate blood while taking mycophenolate mofetil and for at least 6 weeks after stopping mycophenolate mofetil.
- You should not donate sperm while taking mycophenolate mofetil and for 90 days after stopping mycophenolate mofetil.
- Mycophenolate mofetil may influence your ability to drive and use machines (See **"What are the possible side effects of mycophenolate mofetil?"**). If you experience drowsiness, confusion, dizziness, tremor, or low blood pressure during treatment with mycophenolate mofetil, you should be cautious about driving or using heavy machines.

What are the possible side effects of mycophenolate mofetil?
Mycophenolate mofetil may cause serious side effects, including:

- See **"What is the most important information I should know about mycophenolate mofetil?"**
- **Low blood cell counts.** People taking high doses of mycophenolate mofetil each day may have a decrease in blood counts, including:
  - **white blood cells, especially neutrophils.** Neutrophils fight against bacterial infections. You have a higher chance of getting an infection when your white blood cell count is low. This is most common from 1 month to 6 months after your transplant.
  - **red blood cells.** Red blood cells carry oxygen to your body tissues. You have a higher chance of getting severe anemia when your red blood cell count is low.
  - **platelets.** Platelets help with blood clotting.

Your doctor will do blood tests before you start taking mycophenolate mofetil and during treatment with mycophenolate mofetil to check your blood cell counts. Tell your doctor right away if you have any signs of infection (See **"What is the most important information I should know about mycophenolate mofetil?"**), including any unexpected bruising or bleeding. Also, tell your doctor if you have unusual tiredness, lack of energy, dizziness or fainting.

- **Stomach problems.** Stomach problems including intestinal bleeding, a tear in your intestinal wall (perforation) or stomach ulcers can happen in people who take mycophenolate mofetil. Bleeding can be severe and you may have to be hospitalized for treatment. Call your doctor right away if you have sudden or severe stomach-area pain or stomach-area pain that does not go away, or if you have diarrhea.
- **Inflammatory reactions.** Some people taking mycophenolate mofetil may have an inflammatory reaction with fever, joint stiffness, joint pain, and muscle pain. Some of these reactions can be hospitalization. This reaction could happen within weeks to months after your treatment with mycophenolate mofetil starts or if your dose is increased. Call your doctor right away if you experience these symptoms.
- **Allergic (hypersensitivity)** reactions. Allergic reactions, including a severe allergic reaction called anaphylaxis, can happen after taking mycophenolate mofetil. Stop taking mycophenolate mofetil and get emergency medical help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of the face, lips, tongue, or throat
  - rash, hives, or itchinginfections
  - fainting, dizziness, feeling lightheaded
  - trouble breathing or swallowing
  - fast heartbeat
  - chest pain

The most common side effects of mycophenolate mofetil include:

- diarrhea
- blood problems including low white and red blood cell counts
- infections
- blood pressure problems
- fast heartbeat
- swelling of the lower legs, ankles and feet
- changes in laboratory blood levels, including high levels of blood sugar (hyperglycemia)
- stomach problems including diarrhea, constipation, nausea and vomiting
- rash
- nervous system problems such as headache, dizziness and tremor

Side effects that can happen more often in children than in adults taking mycophenolate mofetil include:

- stomach area pain
- fever
- infection
- pain
- blood infection (sepsis)
- diarrhea
- vomiting
- sore throat
- colds (respiratory tract infections)
- high blood pressure
- low white blood cell count
- low red blood cell count

These are not all of the possible side effects of mycophenolate mofetil. Tell your doctor about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com.

How should I store mycophenolate mofetil capsules and tablets?

- Store mycophenolate mofetil capsules and tablets at room temperature between 20° to 25°C (68° to 77°F).
- Keep mycophenolate mofetil tablets in the light resistant container that it comes in.

Keep mycophenolate mofetil and all medicines out of the reach of children.

General Information about the safe and effective use of mycophenolate mofetil.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use mycophenolate mofetil for a condition for which it was not prescribed. Do not give mycophenolate mofetil to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about mycophenolate mofetil. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist about mycophenolate mofetil that is written for health professionals.

What are the ingredients in mycophenolate mofetil capsules and tablets?
Active Ingredient: mycophenolate mofetil
Inactive Ingredients:

Mycophenolate mofetil 250 mg capsules: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone (K-30). The capsule shells contain FD&C red # 3, gelatin, sodium lauryl sulfate, titanium dioxide and yellow iron oxide.

Mycophenolate mofetil 500 mg tablets: croscarmellose sodium, magnesium stearate (Vegetable), microcrystalline cellulose, opadry brown, povidone [K-30].

The opadry brown contains FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, hypromellose, iron oxide red, polyethylene glycol and titanium dioxide.

Distributed by:
Strides Pharma Inc.
Bridgewater, NJ 08807

Revised: 12/2025 OC-036-01-02

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Male Patients
Genotoxic effects have been observed in animal studies at exposures exceeding the human therapeutic exposures by approximately 1.25 times. Thus, the risk of genotoxic effects on sperm cells cannot be excluded. Based on this potential risk, sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment. Also, based on the potential risk of genotoxic effects, male patients should not donate sperm during treatment with mycophenolate mofetil and for at least 90 days after cessation of treatment *[see Use in Special Populations (8.1), Nonclinical Toxicology (13.1), Patient Counseling Information (17.9)]*.

8.4 Pediatric Use
Safety and effectiveness have been established in pediatric patients 3 months and older for the prophylaxis of organ rejection of allogenic kidney, heart or liver transplants.

Kidney Transplant
Use of mycophenolate mofetil in this population is supported by evidence from adequate and well-controlled studies of mycophenolate mofetil in adults with additional data from one open-label, pharmacokinetic and safety study of mycophenolate mofetil in pediatric patients after receiving allogenic kidney transplant (100 patients, 3 months to 18 years of age) *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*.

Heart Transplant and Liver Transplant
Use of mycophenolate mofetil in pediatric heart transplant and liver transplant patients is supported by adequate and well-controlled studies and pharmacokinetic data in adult heart transplant and liver transplant patients. Additional supportive data include pharmacokinetic data in pediatric kidney transplant and pediatric liver transplant patients (8 liver transplant patients, 9 months to 5 years of age, in an open-label, pharmacokinetic and safety study) and published evidence of clinical efficacy and safety in pediatric heart transplant and pediatric liver transplant patients *[see Dosage and Administration (2.3, 2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)]*.

8.5 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 geriatric and younger patients. In general, dose selection for a geriatric patient should take into consideration the presence of decreased hepatic, renal or cardiac function and of concomitant drug therapies *[see Adverse Reactions (6.1), Drug Interactions (7)]*.

8.6 Patients with Renal Impairment
Patients with Kidney Transplant
No dosage adjustments are needed in kidney transplant patients experiencing delayed graft function postoperatively but patients should be carefully monitored *[see Clinical Pharmacology (12.3)]*. In kidney transplant patients with severe chronic impairment of the graft (GFR <25 mL/min/1.73 m^2), no dose adjustments are necessary; however, doses greater than 1 g administered twice a day should be avoided.

Patients with Heart and Liver Transplant
No data are available for heart or liver transplant patients with severe chronic renal impairment. Mycophenolate mofetil may be used for heart or liver transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

8.7 Patients with Hepatic Impairment
Patients with Kidney Transplant
No dosage adjustments are recommended for kidney transplant patients with severe hepatic parenchymal disease. However, it is not known whether dosage adjustments are needed for hepatic disease with other etiologies *[see Clinical Pharmacology (12.3)]*.

Patients with Heart Transplant
No data are available for heart transplant patients with severe hepatic parenchymal disease.

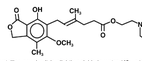
10 OVERDOSAGE
Possible signs and symptoms of acute overdose include hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, and dyspepsia.

The experience with overdose of mycophenolate mofetil in humans is limited. The reported effects associated with overdose fall within the known safety profile of the drug. The highest dose administered to kidney transplant patients in clinical trials has been 4 g/day. In limited experience with heart and liver 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, particularly neutropenia *[see Warnings and Precautions (5.4)]*.

Treatment and Management
MPA and the phenolic glucuronide metabolite of MPA (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 (12.3)]*.

11 DESCRIPTION
Mycophenolate mofetil is an antimetabolite immunosuppressant. It 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-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



MMF 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 3.6). 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 MMF are 5.6 for the morpholino group and 8.5 for the phenolic group.

MMF 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 mofetil is available for oral administration as capsules containing 250 mg of MMF, tablets containing 500 mg of MMF.

Inactive ingredients in mycophenolate mofetil capsules, USP 250 mg include croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone (K-30). The capsule shells contain FD&C red # 3, gelatin, sodium lauryl sulfate, titanium dioxide and yellow iron oxide.

Inactive ingredients in mycophenolate mofetil tablets, USP 500 mg include croscarmellose sodium, magnesium stearate (Vegetable), microcrystalline cellulose, opadry brown, povidone [K-30].

The opadry brown contains FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, hypromellose, iron oxide red, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Mycophenolate mofetil (MMF) is absorbed following oral administration and hydrolyzed to mycophenolic acid (MPA), the active metabolite. MPA is a selective uncompetitive inhibitor of the two isoforms (type I and type II) of inosine monophosphate dehydrogenase (IMPDH) leading to inhibition of the *de novo* pathway of guanosine nucleotide synthesis and blocks DNA synthesis. The mechanism of action of MPA in multifaceted and includes effects on cellular checkpoints responsible for metabolic programming of lymphocytes. MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes. In vitro studies suggest that MPA modulates transcriptional activities in human CD4+ T-lymphocytes by suppressing the Akt/mTOR and STAT5 pathways that are relevant to metabolism and survival, leading to an anergic state of T-cells whereby the cells become less responsive to antigenic stimulation. Additionally, MPA enhanced the expression of negative co-stimulators such as CD70, PD-1, CTLA-4, and transcription factor FoxP3 as well as decreased the expression of positive co-stimulators CD27 and CD28.

MPA decreases proliferative responses of T- and B-lymphocytes to both mitogenic and allo-antigenic stimulation, antibody responses, as well as the production of cytokines from lymphocytes and monocytes such as GM-CSF, IFN-γ, IL-17, and IL-10. Additionally, 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.

Overall, the effect of MPA is cytostatic and reversible.

12.2 Pharmacodynamics
There is a lack of information regarding the pharmacodynamic effects of MMF.

12.3 Pharmacokinetics
Absorption
Following oral and intravenous administration, MMF undergoes complete conversion to MPA, the active metabolite. In 12 healthy volunteers, the mean absolute bioavailability of oral MMF relative to intravenous MMF was 94%. Two 500 mg mycophenolate mofetil tablets have been shown to be bioequivalent to four 250 mg mycophenolate mofetil capsules. Five mL of the 200 mg/mL constituted mycophenolate mofetil oral suspension have been shown to be bioequivalent to four 250 mg capsules.

The mean (±SD) pharmacokinetic parameters estimates for MPA following the administration of MMF given as single doses to healthy volunteers, and multiple doses to kidney, heart, and liver transplant patients, are shown in **Table 10**. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5g twice daily) (see **Table 10**).

Table 10 Pharmacokinetic Parameters for MPA (mean (±SD)) Following Administration of MMF to Healthy Volunteers (Single Dose), and Kidney, Heart, and Liver Transplant Patients (Multiple Doses)

Healthy Volunteers	Dose/Route	T_{max} (h)	C_{max} (mcg/mL)	Total AUC (mcg·h/mL)
Single dose	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Kidney Transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC (0-12h) (mcg·h/mL)**
5 days	1 g/iv	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 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (Less than 40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (Less than 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 (Greater than 3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Heart transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (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 (±6.8) (n=11)	43.3 (±20.6) (n=9)
Late (Greater than 6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1 (±20.4) (n=49)
Liver transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC (0-12h) (mcg·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 (5 to 8 days)	1.5 g/oral	1.15 (±0.432) (n=20)	13.1 (±8.78) (n=20)	29.2 (±11.9) (n=20)
Late (Greater than 6 months)	1.5 g/oral	1.54 (±0.51) (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.

In the early post-transplant period (less than 40 days post-transplant), kidney, heart, and liver transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C_{max} approximately 32% to 44% lower compared to the late transplant period (i.e., 3 to 6 months post-transplant (non-stabilized) for MPA pharmacokinetics).

Mean MPA AUC values following administration of 1 g twice daily intravenous mycophenolate mofetil over 2 hours to kidney transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate post-transplant phase.

In liver transplant patients, administration of 1 g twice daily intravenous mycophenolate mofetil followed by 1.5 g twice daily oral mycophenolate mofetil resulted in mean MPA AUC estimates similar to those found in kidney transplant patients administered 1 g mycophenolate mofetil twice daily.

Effect of Food
Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of MMF when administered at doses of 1.5 g twice daily to kidney transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food *[see Dosage and Administration (2.1)]*.

Distribution
The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers was approximately 3.6 (±1.5) L/kg. At clinically relevant concentrations, MPA is 97% bound to plasma albumin. The phenolic glucuronide metabolite of MPA (MPAG) is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable kidney transplant patients; however, at higher MPAG concentrations (observed in patients with kidney impairment or delayed kidney 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 human serum albumin) and MPAG (at ≥ 460 mcg/mL with plasma proteins) increased 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%.

Elimination
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.

Metabolism
The parent drug, MMF, can be measured systemically during the intravenous infusion; however, approximately 5 minutes after the infusion is stopped or after oral administration, MMF concentrations are below the limit of quantitation (0.4 mcg/mL).

Metabolism to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form MPAG, which is not pharmacologically active. *In vivo*, MPAG is converted to MPA during enterohepatic recirculation.The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of MMF to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Due to the enterohepatic recirculation of MPAG/MPA, secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours post-dose. Bile sequestrants, such as cholestyramine, reduce MPA AUC by interfering with this enterohepatic recirculation of the drug *[see Overdosage (10) and Drug Interaction Studies below]*.

Excretion
Negligible amount of drug is excreted as MPA (less than 1% of dose) in the urine. Orally administered radiolabeled MMF 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.

Increased plasma concentrations of MMF metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency *[see Specific Populations]*.

Specific Populations
Patients with Renal Impairment
The mean (±SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with renal impairment are presented in **Table 11**.

In a single-dose study, MMF was administered as a capsule or as an intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment (GFR < 25 mL/min/1.73 m^2) was about 75% higher relative to that observed in healthy volunteers (GFR > 80 mL/min/1.73 m^2). 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.

Patients with Delayed Graft Function or Nonfunction
In patients with delayed renal graft function post-transplant, mean MPA AUC(0-12h) was comparable to that seen in post-transplant 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 post-transplant patients without delayed renal graft function *[see Dosage and Administration (2.5)]*.

In eight patients with primary graft non-function following kidney 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 MMF 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.

Patients with Hepatic Impairment
The mean (± SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with hepatic impairment is presented in **Table 11**.

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.

Table 11 Pharmacokinetic Parameters for MPA (mean (±SD)) Following Single Doses of MMF Capsules in Chronic Renal and Hepatic Impairment

Pharmacokinetic Parameters for Renal Impairment				
	Dose	**T_{max} (h)**	**C_{max} (mcg/mL)**	**AUC(0-96h) (mcg·h/mL)**
Healthy Volunteers GFR greater than 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 (±12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m^2 (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR less than 25 mL/min/1.73 m^2 (n=7)	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Pharmacokinetic Parameters for Hepatic Impairment				
	Dose	**T_{max} (h)**	**C_{max} (mcg/mL)**	**AUC(0-48h) (mcg·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)	29.8 (±10.7)

Pediatric Patients
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^2 twice daily (up to a maximum of 1 g twice daily) after allogeneic kidney transplantation. The pharmacokinetic data for MPA is provided in **Table 12**.

Table 12 Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time after Allogeneic Kidney Transplantation

Age Group	(n)	Time	T_{max} (h)	Dose Adjusted[a] C_{max} (mcg/mL)	Dose Adjusted[a] AUC_{12} (mcg·h/mL)
1 to less than 2 yr	(6)[c]	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to less than 6 yr	(17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to less than 12 yr	(16)		0.940 (0.546)	13.1 (6.30)	33.2 (12.1)
12 to 18 yr	(21)		1.16 (0.830)	11.7 (10.7)	26.3 (9.14)[d]
1 to less than 2 yr	(4)[c]	Late (Month 3)	0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to less than 6 yr	(15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to less than 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)[f]
1 to less than 2 yr	(4)[c]	Late (Month 9)	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to less than 6 yr	(12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to less than 12 yr	(11)		1.12 (0.462)	29.2 (12.6)	66.8 (21.2)
12 to 18 yr	(14)		1.09 (0.518)	18.1 (7.29)	56.7 (14.0)

[a] adjusted to a dose of 600 mg/m^2
[c] n=20
[d] n=16
[f] a subset of 1 to <6 yr

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

A comparison of dose-normalized (to 600 mg/m^2) MPA AUC values in 12 pediatric kidney transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 pediatric liver transplant patients (median age 17 months (range: 10 – 60 months)) and at 6 months and beyond post-transplant revealed that, at the same dose, there were on average 23% lower AUC values in the pediatric liver compared to pediatric kidney patients. This is consistent with the need for higher dosing in adult liver transplant patients compared to kidney transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of mycophenolate mofetil, there is similar MPA exposure among kidney transplant and heart transplant patients. Based on the established similarity in MPA exposure between pediatric kidney transplant and adult kidney transplant patients at their respective approved doses, it is expected that MPA exposure at the recommended dosage will be similar in pediatric heart transplant and adult heart transplant patients.

Male and Female Patients
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) mcg·h/mL while mean (±SD) MPA C_{max} 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.

Geriatric Patients
The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in geriatric transplant patients when compared to younger transplant patients.

Drug Interaction Studies
Acyclovir
Coadministration of MMF (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and C_{max}. However, MPAG and acyclovir plasma AUCs were increased 19.6% and 21.9%, respectively.

Antacids with Magnesium and Aluminum Hydroxides
Absorption of a single dose of MMF (2 g) was decreased when administered to 10 rheumatoid arthritis patients also taking Maalox® TC (10 mL qid). The C_{max} and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when MMF was administered alone under fasting conditions.

Proton Pump Inhibitors (PPIs)
Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving mycophenolate mofetil has been reported to reduce the exposure to MPA. An approximate reduction of 30 to 70% in the C_{max} and 25% to 35% in the AUC of MPA has been observed, possibly due to a decrease in MPA solubility at an increased gastric pH.

Cholestyramine
Following single-dose administration of 1.5 g MMF to 12 healthy volunteers pretreated with 4 g three times a day 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.

Cyclosporine
Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g twice daily of MMF in 10 stable kidney transplant patients. The mean (±SD) AUC(0-12h) and C_{max} of cyclosporine after 14 days of multiple doses of MMF 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 MMF.
Cyclosporine A interferes with MPA enterohepatic recirculation. In kidney transplant patients, mean MPA exposure (AUC(0-12h)) was approximately 30-50% greater when MMF was administered without cyclosporine compared with when MMF was 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.

Drugs Affecting Glucuronidation
Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA AUC(0-∞) by 35% was observed with concomitant administration of isavuconazole).

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease in MPA concentrations. Telmisartan changes MPR's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and glucuronidation activity.

Ganciclovir
Following single-dose administration to 12 stable kidney transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} (n=10) were 54.3 (±19.0) mcg•h/mL and 11.5 (±1.8) mcg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (±17.0) mcg•h/mL and 10.6 (±2.0) mcg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and C_{max} 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) µg•h/mL and 30.9 (±11.2) mcg/mL, respectively, after administration of MMF alone.

Oral Contraceptives
A study of coadministration of mycophenolate mofetil (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean serum levels of LH, FSH and progesterone not significantly affected. 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.

Sevelamer
Concomitant administration of sevelamer and MMF in adult and pediatric patients decreased the mean MPA C_{max} and AUC (0-12h) by 36% and 26% respectively.

Antimicrobials
Antimicrobials eliminating beta-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antimicrobials) may interfere with the MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning antibiotics is as follows:

- Trimethoprim/Sulfamethoxazole: Following single-dose administration of MMF (1.5 g) to 12 healthy male volunteers on day 8 of a 10-day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered twice daily, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (±19.8) mcg•h/mL and 34.0 (±6.6) µg/mL, respectively, compared to 79.2 (±27.9) mcg•h/mL and 34.2 (±10.7) mcg/mL, respectively, after administration of MMF alone.
- Norfloxacin and Metronidazole: Following single-dose administration of MMF (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(0-48h) was significantly reduced by 33% compared to the administration of MMF alone (p<0.05). The mean (±SD) MPA AUC(0-48h) after coadministration of MMF with norfloxacin or metronidazole separately was 48.3 (±24) mcg