PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Mycophenolate Mofetil for Injection USP

500 mg / vial mycophenolate mofetil
(as mycophenolate mofetil hydrochloride)

Sterile Lyophilized Powder

Immunosuppressive Agent

SteriMax Inc.
2770 Portland Drive
Oakville, ON L6H 6R4

Date of Initial Authorization: August 8, 2018

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Submission Control No: 252956

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Immune	10-2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Mycophenolate Mofetil for Injection USP (mycophenolate mofetil) is indicated for:

Adults

- The prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate Mofetil for Injection USP should be used concomitantly with cyclosporine and corticosteroids.

- Mycophenolate Mofetil for Injection USP (mycophenolate mofetil hydrochloride for intravenous infusion) is an alternative dosage form to mycophenolate mofetil capsules, tablets and oral suspension. Mycophenolate Mofetil for Injection USP should be administered within 24 hours following transplantation. Mycophenolate Mofetil for Injection USP can be administered for up to 14 days; patients should be switched to oral mycophenolate mofetil as soon as they can tolerate oral medication.

1.1 Pediatrics (2-18 years of age)

- Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in pediatric patients (2 to 18 years) receiving allogeneic renal transplants. Mycophenolate Mofetil for Injection USP should be used concomitantly with cyclosporine and corticosteroids.

1.2 Geriatrics

- No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Mycophenolate Mofetil for Injection USP is contraindicated in patients with a known hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Mycophenolate Mofetil for Injection USP is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN) (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Mycophenolate Mofetil for Injection USP is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see WARNINGS and PRECAUTIONS).
- Mycophenolate Mofetil for Injection USP is contraindicated in women of childbearing potential not using highly effective contraceptive methods and without providing a pregnancy test result (see WARNINGS and PRECAUTIONS).
- Mycophenolate Mofetil for Injection USP is contraindicated in women who are breastfeeding (see WARNINGS and PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- There have been reports of first trimester pregnancy loss and congenital malformations following the use of mycophenolate mofetil in combination with other immunosuppressants during pregnancy (see WARNINGS and PRECAUTIONS).

- Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use Mycophenolate Mofetil for Injection USP (mycophenolate mofetil). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Mycophenolate Mofetil for Injection USP (mycophenolate mofetil) should be used concomitantly with standard cyclosporine and corticosteroid therapy.
- Mycophenolate Mofetil for Injection USP is an alternative dosage form to mycophenolate mofetil capsules and tablets recommended for patients unable to take mycophenolate mofetil capsules or tablets. Mycophenolate Mofetil for Injection USP should be administered within 24 hours following transplantation. Mycophenolate Mofetil for Injection USP can be administered for up to 14 days; patients should be switched to oral mycophenolate mofetil as soon as they can tolerate oral medication.
- **Caution: Mycophenolate Mofetil for Injection USP solution should never be administered by rapid or bolus intravenous injection.**

4.2 Recommended Dose and Dosage Adjustment

Adults

Renal Transplantation

A dose of 1 g administered intravenously (over 2 hours) 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 per day of mycophenolate mofetil in these trials demonstrated an overall better safety profile than did patients receiving 3 g per day of mycophenolate mofetil.

Cardiac Transplantation

A dose of 1.5 g twice daily administered intravenously (over **no less than 2 hours**) is recommended for use in adult cardiac transplant patients.

Hepatic Transplantation

A dose of 1 g twice daily administered intravenously (over **no less than 2 hours**) is recommended for use in adult hepatic transplant patients.

***Pediatrics (2 to 18 years)**

The recommended dose of mycophenolate mofetil oral suspension for renal transplant patients is 600 mg/m^2 body surface area twice daily (up to a maximum of 2 g daily).

Patients with a body surface area of 1.25 to 1.5 m^2 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 m^2 may be dosed with mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

*** There is no data for the mycophenolate mofetil intravenous infusion (IV infusion) in children.**

Dosage Adjustment

Renal Impairment
In renal transplant patients with severe chronic renal impairment (GFR <25mL/min/1.73m^2) outside the immediate post-transplant period, doses of mycophenolate mofetil greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed (see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. Mycophenolate mofetil should be used for cardiac or he patic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

If neutropenia develops (ANC <1.3 x $10^3/\mu L$), dosing with mycophenolate mofetil should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. (See WARNINGS AND PRECAUTIONS: Immune, Monitoring and Laboratory Tests and ADVERSE REACTIONS).

Delayed Renal Graft Function Post Transplant
No dose adjustment is recommended for these patients, however, they should be carefully observed (see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

4.3 Reconstitution

Parenteral Products:
Preparation of Infusion Solution (6 mg / mL)

Mycophenolate Mofetil for Injection USP does not contain an antibacterial preservative; therefore reconstitution and dilution of the product must be performed under aseptic conditions.

Mycophenolate Mofetil for Injection USP infusion solution must be prepared in two steps: the first step is a reconstitution step with 5% Dextrose Injection, USP and the second step is a dilution step with 5% Dextrose Injection, USP. A detailed description of the preparation is given below:

Step 1

a. Two (2) vials of Mycophenolate Mofetil for Injection USP are used for preparing each 1 g dose, whereas three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial by injecting 14 mL of 5% Dextrose Injection, USP.
b. Gently shake the vial to dissolve the drug.
c. Inspect the resulting slightly yellow solution for particulate matter and discoloration prior to further dilution. Discard the vial if particulate matter or discoloration is observed.

Step 2

a. To prepare a 1 g dose, further dilute the contents of the two reconstituted vials (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection, USP. To prepare a 1.5 g dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL) into 210 mL of 5% Dextrose Injection, USP. The final concentration of both solutions is 6 mg mycophenolate mofetil per mL.
b. As with all parenteral drug products, diluted solution should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours from reconstitution and dilution of the drug product. Keep reconstituted and further diluted, infusion solution at 15ºC to 30ºC.

Mycophenolate Mofetil for Injection USP should not be mixed or administered concurrently via the same infusion catheter with other intravenous drugs or infusion admixtures.

4.4 Administration

Mycophenolate Mofetil for Injection USP must be reconstituted and diluted to a concentration of 6 mg / mL using 5% Dextrose Injection, USP (see DOSAGE AND ADMINISTRATION:

Reconstitution, Preparation of Infusion Solutions). Mycophenolate Mofetil for Injection USP is incompatible with other intravenous infusion solutions. **Following reconstitution, Mycophenolate Mofetil for Injection USP solution must be administered by slow intravenous infusion over a period of no less than 2 hours by either peripheral or central vein.**

5 OVERDOSAGE

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

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see WARNINGS AND PRECAUTIONS: Immune). If neutropenia develops, dosing with Mycophenolate Mofetil for Injection USP should be interrupted or the dose reduced (see WARNINGS AND PRECAUTIONS: Immune).

The highest dose administered to renal transplant patients in clinical trials has been 4 g per day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g or 5 g per day. At doses of 4 g or 5 g per day, there appears to be a higher rate, compared to the use of 3 g per 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.

At clinically encountered concentrations, MPA and MPAG are not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 mcg/mL), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants, such as cholestyramine reduce the MPA AUC.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Lyophilized powder /	Polysorbate 80 (TWEEN)

	500 mg/vial (as hydrochloride)	(See CONTRAINDICATIONS)

Description

Composition: Mycophenolate Mofetil for Injection USP is available as a sterile white to off-white lyophilized cake/powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of Mycophenolate Mofetil for Injection USP contains the equivalent of 500 mg mycophenolate mofetil as mycophenolate mofetil hydrochloride. The non-medicinal ingredients are citric acid, 5 mg, hydrochloric acid, 45.625 mg, polysorbate 80, 25 mg, and sodium hydroxide and/or hydrochloric acid to adjust pH.

Availability: Mycophenolate Mofetil for Injection USP is supplied in a 20 mL, sterile vial closed with a rubber stopper not made with natural rubber latex, containing the equivalent of 500 mg mycophenolate mofetil (as mycophenolate mofetil hydrochloride), as the hydrochloride salt in cartons of 4 vials. Each vial is intended for single use only.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Caution: Mycophenolate Mofetil for Injection USP should never be administered by rapid or bolus intravenous injection.

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with mycophenolic acid (MPA) enterohepatic recirculation e.g. cyclosporine to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure (See DRUG INTERACTIONS). Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, sevelamer, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of Mycophenolate Mofetil for Injection USP (see Drug-Drug Interactions). Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

It is recommended that Mycophenolate Mofetil for Injection USP (mycophenolate mofetil) should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

Blood Donation

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of Mycophenolate Mofetil for Injection USP.

Carcinogenesis and Mutagenesis

Neoplasms

Patients receiving Mycophenolate Mofetil for Injection USP, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As with all patients at an increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor (see ADVERSE REACTIONS).

Driving and Operating Machinery

Mycophenolate Mofetil for Injection USP may have a moderate influence on the ability to drive and use machines.

Patients should be advised to use caution when driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with Mycophenolate Mofetil for Injection USP.

Endocrine and Metabolism

Mycophenolate mofetil is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, therefore it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Gastrointestinal

Mycophenolate Mofetil for Injection USP should be administered with caution in patients with active serious digestive system disease. Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac and in 5.4% of hepatic transplant patients treated with mycophenolate mofetil 3 g daily. Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including

infrequent cases of gastrointestinal tract ulceration, and rarely perforation (colon, gall bladder). Most patients receiving mycophenolate mofetil were also receiving other drugs that are known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil.

Hematologic

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

Patients receiving Mycophenolate Mofetil for Injection USP should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients receiving Mycophenolate Mofetil for Injection USP should be monitored for neutropenia. Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION: Dosage Adjustment). The development of neutropenia may be related to Mycophenolate Mofetil for Injection USP itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (absolute neutrophil count [ANC] < 1.3 x 10^3/µL), dosing with mycophenolate mofetil should be interrupted or the dose should be reduced, appropriate diagnostic tests performed, and the patient managed appropriately. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant for patients treated for prevention of renal, cardiac and hepatic rejection.

Severe neutropenia (ANC < 0.5 x 10^3/µL) developed in up to 2.0% of renal, up to 2.8% of cardiac and up to 3.6% hepatic transplant patients receiving mycophenolate mofetil 3 g daily (see ADVERSE REACTIONS).

Immune

Mycophenolate mofetil has been administered in combination with the following agents in clinical trials: anti-thymocyte globulin [equine] (Atgam®) induction, muromonab-CD3 (Orthoclone OKT®3), cyclosporine (Sandimmune®, Neoral®), and corticosteroids. The efficacy

and safety of the use of mycophenolate mofetil in combination with other immunosuppressive agents has not been determined.

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants.

Cases of progressive multifocal leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in mycophenolate mofetil treated patients. The reported cases had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

BK virus-associated nephropathy has been observed during the use of mycophenolate mofetil in patients post renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Due to the cytostatic effect of mycophenolate mofetil on B- and T-lymphocytes, increased severity of COVID-19 may occur. Dose reduction or discontinuation of Mycophenolate Mofetil for Injection USP in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy, or in cases of clinically significant COVID-19.

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 ADVERSE REACTIONS).

Monitoring and Laboratory Tests

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see WARNINGS AND PRECAUTIONS: Immune and DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Mycophenolate Mofetil for Injection USP (see WARNINGS AND PRECAUTIONS: Immune). Patients should be given complete dosage instructions and informed of the increased

risk of lymphoproliferative disease and certain other malignancies.

Renal

Administration of doses of mycophenolate mofetil greater than 1 g administered twice a day to renal transplant patients with severe chronic renal impairment (GFR < 25 mL/min/1.73m^2) should be avoided and patients should be carefully observed (see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency and DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

No data are available for cardiac or hepatic transplant patients with severe chronic, renal impairment. Mycophenolate Mofetil for Injection USP should be used for cardiac or hepatic transplant patients with severe, chronic, renal impairment if the potential benefits outweigh the potential risks.

Reproductive Health: Female and Male Potential

- **Fertility**

Mycophenolate Mofetil for Injection USP is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see CONTRAINDICATIONS).

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning. Women of child bearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning Mycophenolate Mofetil for Injection USP therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Prior to starting therapy with Mycophenolate Mofetil for Injection USP, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; the second test should be performed 8-10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Limited clinical evidence is currently available on paternal exposure to mycophenolate mofetil. Based on the animal data, the risk of genotoxic effects on sperm cells cannot completely be excluded. In absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is

recommended: 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. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

Men should not donate semen during therapy and for 90 days following discontinuation of Mycophenolate Mofetil for Injection USP.

7.1 Special Populations

7.1.1 Pregnant Women

Mycophenolate Mofetil for Injection USP is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods and without providing a pregnancy test result (see CONTRAINDICATIONS and Post-Market Adverse Reactions). Mycophenolate Mofetil for Injection USP is a powerful teratogen and mutagen. Spontaneous abortion (rate of 45-49% compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants) and congenital malformations (estimated rate of 23-27%) have been reported following MMF exposure during pregnancy (see Post-Market Adverse Reactions). For comparison the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4 to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.

Studies in animals have shown reproductive toxicity (see TOXICOLOGY: Reproductive and Developmental Toxicity).

<u>Labor and delivery</u>

The safe use of Mycophenolate Mofetil for Injection USP during labor and delivery has not been established.

7.1.2 Breast-feeding

Mycophenolate Mofetil for Injection USP is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see CONTRAINDICATIONS). Studies in rats have shown mycophenolate mofetil is excreted in milk. It is not known whether this drug is excreted in human milk.

7.1.3 Pediatrics

Safety and efficacy in children receiving allogeneic cardiac or hepatic transplants have not been established.

For pediatric patients receiving renal transplants also see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions, Pediatrics; CLINICAL TRIALS; ADVERSE REACTIONS: Clinical Trial Adverse Reactions - Pediatrics; and DOSAGE AND ADMINISTRATION: Pediatrics.

7.1.4 Geriatrics

Geriatric patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse event profile associated with the use of immunosuppressive drugs is often difficult to establish owing to the presence of underlying disease and the concurrent use of many other medications. The principal adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections.

The adverse event profile associated with the administration of intravenous mycophenolate mofetil (mycophenolate for injection) has been shown to be similar to that observed after administration of oral dosage forms of mycophenolate mofetil.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Mycophenolate Mofetil (oral)

The incidence of adverse events for mycophenolate mofetil was determined in randomized comparative double-blind trials in prevention of rejection in renal (2 active, 1 placebo controlled trials), cardiac (1 active controlled trial) and hepatic (1 active controlled trial) transplant patients.

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 renal patients, 65% of the cardiac patients and 45% of the hepatic patients have been treated for more than one year.

Adverse events, whether or not deemed to be causally associated with the study medication, reported in ≥ 10% of patients in treatment groups are presented below.

Table 2 Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥10% of Adult Patients Randomized to Mycophenolate Mofetil)

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 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	17.6	19.7	15.6	18.7	18.7	27.4	26.5
Asthenia	13.7	16.1	19.9	43.3	36.3	35.4	33.8
Chest pain	13.4	13.3	14.7	26.3	26.0	15.9	13.2
Back pain	11.6	12.1	14.1	34.6	28.4	46.6	47.4
Accidental injury	-	-	-	19.0	14.9	11.2	15.0
Chills	-	-	-	11.4	11.4	10.8	10.1

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day
Ascites	-	-	-	-	-	24.2	22.6
Abdomen enlarged	-	-	-	-	-	18.8	17.8
Hernia	-	-	-	-	-	11.6	8.7
Peritonitis	-	-	-	-	-	10.1	12.5
Cardiovascular							
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6
Hypotension	-	-	-	32.5	36.0	18.4	20.9
Cardiovascular disorder	-	-	-	25.6	24.2	-	-
Tachycardia	-	-	-	20.1	18.0	22.0	15.7
Arrhythmia	-	-	-	19.0	18.7	-	-
Bradycardia	-	-	-	17.3	17.3	-	-
Pericardial effusion	-	-	-	15.9	13.5	-	-
Heart failure	-	-	-	11.8	8.7	-	-
Digestive							
Diarrhea	31.0	36.1	20.9	45.3	34.3	51.3	49.8
Constipation	22.9	18.5	22.4	41.2	37.7	37.9	38.3
Nausea	19.9	23.6	24.5	54.0	54.3	54.5	51.2
Dyspepsia	17.6	13.6	13.8	18.7	19.4	22.4	20.9
Vomiting	12.5	13.6	9.2	33.9	28.4	32.9	33.4
Nausea and vomiting	10.4	9.7	10.7	11.1	7.6	-	-
Oral moniliasis	10.1	12.1	11.3	11.4	11.8	10.1	10.1
Flatulence	-	-	-	13.8	15.6	12.6	9.8
Anorexia	-	-	-	-	-	25.3	17.1
Liver function tests abnormal	-	-	-	-	-	24.9	19.2
Cholangitis	-	-	-	-	-	14.1	13.6
Hepatitis	-	-	-	-	-	13.0	16.0
Cholestatic jaundice	-	-	-	-	-	11.9	10.8
Hemic 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	39.1	45.8	39.0
Thrombocytopenia	10.1	8.2	13.2	23.5	27.0	38.3	42.2

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day
Hypochromic anemia	7.4	11.5	9.2	24.6	23.5	13.7	10.8
Leukocytosis	7.1	10.9	7.4	40.5	35.6	22.4	21.3
Ecchymosis	-	-	-	16.6	8.0	-	-
Metabolic and Nutritional							
Peripheral edema	28.6	27.0	28.2	64.0	53.3	48.4	47.7
Hypercholesteremia	12.8	8.5	11.3	41.2	38.4	-	-
Hypophosphatemia	12.5	15.8	11.7	-	-	14.4	9.1
Edema	12.2	11.8	13.5	26.6	25.6	28.2	28.2
Hypokalemia	10.1	10.0	8.3	31.8	25.6	37.2	41.1
Hyperkalemia	8.9	10.3	16.9	14.5	19.7	22	23.7
Hyperglycemia	8.6	12.4	15.0	46.7	52.6	43.7	48.8
Creatinine increased	-	-	-	39.4	36.0	19.9	21.6
BUN increased	-	-	-	34.6	32.5	10.1	12.9
Lactic dehydrogenase increased	-	-	-	23.2	17	-	-
Bilirubinemia	-	-	-	18	21.8	14.4	18.8
Hypervolemia	-	-	-	16.6	22.8	-	-
Generalized edema	-	-	-	18.0	20.1	14.8	16
Hyperuricemia	-	-	-	16.3	17.6	-	-
SGOT increased	-	-	-	17.3	15.6	-	-
Hypomagnesemia	-	-	-	18.3	12.8	39	37.6
Acidosis	-	-	-	14.2	16.6	-	-
Weight gain	-	-	-	15.6	15.2	-	-
SGPT increased	-	-	-	15.6	12.5	-	-
Hyponatremia	-	-	-	11.4	11.8	-	-
Hyperlipemia	-	-	-	10.7	9.3	-	-
Hypocalcemia	-	-	-	-	-	30	30
Hypoproteinemia	-	-	-	-	-	13.4	13.9
Hypoglycemia	-	-	-	-	-	10.5	9.1
Healing abnormal	-	-	-	-	-	10.5	8.7
Musculoskeletal							

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day
System							
Leg cramps	-	-	-	16.6	15.6	-	-
Myasthenia	-	-	-	12.5	9.7	-	-
Myalgia	-	-	-	12.5	9.3	-	-
Nervous System							
Tremor	11.0	11.8	12.3	24.2	23.9	33.9	35.5
Insomnia	8.9	11.8	10.4	40.8	37.7	52.3	47.0
Dizziness	5.7	11.2	11.0	28.7	27.7	16.2	14.3
Anxiety	-	-	-	28.4	23.9	19.5	17.8
Paresthesia	-	-	-	20.8	18.0	15.2	15.3
Hypertonia	-	-	-	15.6	14.5	-	-
Depression	-	-	-	15.6	12.5	17.3	16.7
Agitation	-	-	-	13.1	12.8	-	-
Somnolence	-	-	-	11.1	10.4	-	-
Confusion	-	-	-	13.5	7.6	17.3	18.8
Nervousness	-	-	-	11.4	9.0	10.1	10.5
Respiratory							
Infection	22.0	23.9	19.6	37.0	35.3	15.9	19.9
Dyspnea	15.5	17.3	16.6	36.7	36.3	31	30.3
Cough increased	15.5	13.3	15.0	31.1	25.6	15.9	12.5
Pharyngitis	9.5	11.2	8.0	18.3	13.5	14.1	12.5
Lung disorder	-	-	-	30.1	29.1	22	18.8
Sinusitis	-	-	-	26.0	19.0	11.2	9.8
Rhinitis	-	-	-	19.0	15.6	-	-
Pleural effusion	-	-	-	17.0	13.8	34.3	35.9
Asthma	-	-	-	11.1	11.4	-	-
Pneumonia	-	-	-	10.7	10.4	13.7	11.5
Atelectasis	-	-	-	-	-	13	12.9
Skin and Appendages							
Acne	10.1	9.7	6.4	12.1	9.3	-	-
Rash	-	-	-	22.1	18.0	17.7	18.5
Skin disorder	-	-	-	12.5	8.7	-	-
Pruritus	-	-	-	-	-	14.1	10.5

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day
Sweating	-	-	-	-	-	10.8	10.1
Special Senses							
Amblyopia	-	-	-	14.9	6.6	-	-
Urogenital							
Urinary tract infection	37.2	37.0	33.7	13.1	11.8	18.1	17.8
Hematuria	14	12.1	11.3	-	-	-	-
Kidney tubular necrosis	6.3	10.0	5.8	-	-	-	-
Kidney function abnormal	-	-	-	21.8	26.3	25.6	28.9
Oliguria	-	-	-	14.2	12.8	17	20.6

The placebo-controlled renal transplant study generally showed fewer adverse events occurring in ≥10% 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. However, the following adverse events were reported in the placebo-controlled renal transplant study but not reported in the azathioprine-controlled renal transplant studies with an incidence of ≥10%: urinary tract disorder, bronchitis and pneumonia.

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

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

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

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

The incidence of malignancies among the 1,483 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%-1% of patients receiving mycophenolate mofetil (2g or 3g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac and hepatic transplant patients followed for at least 1 year (see WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis). Non-melanoma skin carcinomas occurred in 1.6%-4.2% of patients, other types of malignancy in 0.7%-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.

Severe neutropenia (ANC < 0.5 x 10^3/μL) 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 3g daily (see WARNINGS AND PRECAUTIONS: Immune and Monitoring and Laboratory Tests and DOSAGE ADMINISTRATION: Dosage Adjustment)

The following table shows the incidence of opportunistic infections that occurred in the renal, cardiac and hepatic transplant populations in the azathioprine-controlled prevention trials:

Table 3 Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

	Renal Studies			Cardiac Study		Hepatic Study	
	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day or 100-150 mg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1.5-3 mg/kg/day	Mycophenolate mofetil 3 g/day	Azathioprine 1-2 mg/kg/day
	%	%	%	%	%	%	%
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	18.7	17.6	22.4	24.4
- Muco-cutaneous	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 patients treated with mycophenolate mofetil in the above azathioprine-controlled studies: *Herpes zoster*, visceral disease; *Candida*, urinary tract infection, fungemia/disseminated disease, tissue invasive disease; *Cryptococcosis*; *Aspergillus/Mucor*; *Pneumocystis jiroveci*.

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 AND PRECAUTIONS: Immune).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with mycophenolate mofetil than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with mycophenolate mofetil.

The following adverse events were reported with ≥ 3% - < 10% incidence in renal, cardiac and hepatic transplant patients treated with mycophenolate mofetil, in combination with cyclosporine and corticosteroids.

Mycophenolate Mofetil for Injection

The adverse event profile of mycophenolate mofetil for injection was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of intravenous and oral mycophenolate mofetil in renal transplant patients in the immediate post-transplant period (administered for the first 5 days). The potential venous irritation of mycophenolate mofetil for injection was evaluated by comparing the adverse events attributable to peripheral venous infusion of mycophenolate mofetil for injection with those observed in the IV placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with mycophenolate mofetil for injection.

In the active controlled study in hepatic transplant patients, 2 g/day of mycophenolate mofetil for injection was administered in the immediate posttransplant period (up to 14 days). The safety profile of intravenous mycophenolate mofetil was similar to that of intravenous azathioprine.

8.2.1 *Clinical Trial Adverse Reactions - 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/m^2 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. However, the following treatment-related adverse events occurred with a frequency of ≥10% in children and were more frequent in the pediatric population, particularly in children under 6 years of age, when the frequency of treatment- related adverse events were compared to adults: diarrhea, anemia, leucopenia, sepsis, and infection.

8.3 Less Common Clinical Trial Adverse Reactions

Table 4 Adverse Events Reported in ≥3% - <10% of Adult Patients Treated with Mycophenolate Mofetil in Combination with Cyclosporine and Corticosteroids

Body System	Renal	Cardiac	Hepatic
Body as a whole	abdomen enlarged, accidental injury, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, malaise, pelvic pain	abdomen enlarged, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, malaise, neck pain, pelvic pain	abscess, cellulitis, chills occurring with fever, cyst, flu syndrome, hemorrhage, lab test abnormal, malaise, neck pain
Cardiovascular	angina pectoris, atrial fibrillation, cardiovascular disorder, hypotension, palpitation, peripheral vascular disorder, postural hypotension, tachycardia, thrombosis, vasodilatation	angina pectoris, atrial fibrillation, atrial flutter, congestive heart failure, extrasystole, heart arrest, palpitation, pallor, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased	arrhythmia, arterial thrombosis, atrial fibrillation, bradycardia, palpitation, syncope, vasodilatation
Digestive	anorexia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal hemorrhage,	anorexia, dysphagia, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder,	dysphagia, esophagitis, gastritis, gastrointestinal disorder, gastrointestinal hemorrhage, ileus, infection,

Body System	Renal	Cardiac	Hepatic
	gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, liver function tests abnormal, mouth ulceration, rectal disorder	gingivitis, gum hyperplasia, infection, jaundice, liver damage, liver function tests abnormal, melena, rectal disorder, stomatitis	jaundice, melena, mouth ulceration, nausea and vomiting, rectal disorder, stomach ulcer
Endocrine	diabetes mellitus, parathyroid disorder	Cushing's syndrome, diabetes mellitus, hypothyroidism	diabetes mellitus
Hemic and Lymphatic	ecchymosis, polycythemia	petechia, prothrombin time increased, thromboplastin time increased	coagulation disorder, ecchymosis, pancytopenia, prothrombin time increased
Metabolic and Nutritional	acidosis, alkaline phosphatase increased, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, hypercalcemia, hyperlipemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, lactic dehydrogenase increased, SGOT increased, SGPT increased, weight gain	abnormal healing, alkaline phosphatase increased, alkalosis, dehydration, gout, hypocalcemia, hypochloremia, hypoglycemia, hypoproteinemia, hypophosphatemia, hypovolemia, hypoxia, respiratory acidosis, thirst, weight loss	acidosis, alkaline phosphatase increased, dehydration, hypercholesteremia, hyperlipemia, hyperphosphatemia, hypervolemia, hyponatremia, hypoxia, hypovolemia, SGOT increased, SGPT increased, weight gain, weight loss
Muskoskeletal	arthralgia, joint disorder, leg cramps, myalgia, myasthenia	arthralgia, joint disorder	arthralgia, leg cramps, myalgia, myasthenia, osteoporosis
Nervous	anxiety, depression, hypertonia, paresthesia, somnolence	convulsion, emotional lability, hallucinations, neuropathy, thinking abnormal, vertigo	agitation, convulsion, delirium, dry mouth, hypertonia, hypesthesia, neuropathy, psychosis, thinking abnormal, somnolence
Respiratory	asthma, bronchitis, lung edema, lung disorder, pleural effusion, pneumonia, rhinitis, sinusitis	apnea, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, lung edema, neoplasm, pain, pneumothorax, respiratory disorder, sputum increased, voice alteration	asthma, bronchitis, epistaxis, hyperventilation, lung edema, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis
Skin and Appendages	alopecia, fungal dermatitis, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating	fungal dermatitis, hemorrhage, pruritus, skin benign neoplasm, skin carcinoma, skin hypertrophy, skin ulcer, sweating	acne, fungal dermatitis, hemorrhage, hirsutism, skin benign neoplasm, skin disorder, skin ulcer, vesiculobullous rash
Special Senses	amblyopia, cataract (not specified), conjunctivitis	abnormal vision, conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder	abnormal vision, amblyopia, conjunctivitis, deafness
Urogenital	albuminuria, dysuria, hydronephrosis, impotence,	dysuria, hematuria, impotence, kidney failure,	acute kidney failure, dysuria, hematuria, kidney failure,

Body System	Renal	Cardiac	Hepatic
	pain, pyelonephritis, urinary frequency, urinary tract disorder	nocturia, prostatic disorder, urine abnormality, urinary frequency, urinary incontinence, urinary retention	scrotal edema, urinary frequency, urinary incontinence

8.4 Post-Market Adverse Reactions

The following adverse reactions have been reported from marketing experience with mycophenolate mofetil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: protozoal infections

Neoplasms benign, malignant and unspecified (including cysts and polyps): lymphoma, lymphoproliferative disorder

Blood and lymphatic system disorders: aplasia pure red cell, bone marrow failure

Gastrointestinal disorders: pancreatitis

Immune system disorders: hypersensitivity, hypogammaglobulinemia

Respiratory, thoracic and mediastinal disorders: bronchiectasis, interstitial lung disease, pulmonary fibrosis

Vascular disorders: lymphocele

The following adverse events, not mentioned above, were reported in clinical trials and in postmarketing experience in patients treated with mycophenolate mofetil:

Congenital disorders: Congenital malformations, including multiple malformations, have been reported post marketing in children of female patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy (See WARNINGS and

PRECAUTIONS: Special Populations). The following malformations were most frequently reported:

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

Pregnancy, puerperium and perinatal conditions: Spontaneous abortions have been reported in patients exposed to mycophenolate mofetil (45-49%), mainly in the first trimester (see WARNINGS and PRECAUTIONS: Special Populations).

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

Hemic and Lymphatic: Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. Consideration should be given, in patients developing recurrent infections, to have their serum immunoglobulins measured and monitored as needed.

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of infection such as tuberculosis and atypical mycobacterial infection.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in mycophenolate mofetil treated patients. The reported cases had risk factors for PML, including immunosuppressant therapies and impairment of immune function.

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

Respiratory Disorders: There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal.

Bronchiectasis*:* In adult and pediatric transplant patients treated with mycophenolate mofetil in combination with other immunosuppressants, cases of bronchiectasis have been reported in the published literature. Considerations should be given, in patients developing persistent pulmonary symptoms such as coughing, dyspnea or recurring respiratory infections, to investigate further to determine definitively if they present bronchiectasis. In some literature reported cases, bronchiectasis was reported concurrently with hypogammaglobulinemia.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

It is recommended that Mycophenolate Mofetil for Injection USP (mycophenolate mofetil) should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of mycophenolic acid (MPA) by cholestyramine, caution should be used in the concomitant administration of Mycophenolate Mofetil for Injection USP with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of mycophenolate mofetil.

See WARNINGS AND PRECAUTIONS.

Patients should be advised that during treatment with Mycophenolate Mofetil for Injection USP, vaccinations may be less effective and the use of live attenuated vaccines should be avoided. Prescribers should refer to the Canadian Immunization Guideline for further guidance.

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

9.2 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies have been conducted.

9.3 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Acyclovir: Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to twelve healthy volunteers resulted in no significant change in MPA AUC and C_{max}. However, the phenolic glucuronide of MPA (MPAG) and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug e.g., valacyclovir to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids with magnesium and aluminum hydroxides and proton pump inhibitors (PPIs): Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to rheumatoid arthritis patients also taking Maalox® TC (10 mL four times daily). The C_{max} and AUC values for MPA were 38% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. Mycophenolate Mofetil for Injection USP may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that Mycophenolate Mofetil for Injection USP and the antacid not be administered simultaneously. Decreased mycophenolic acid (MPA) exposure has also been observed when PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. This information from pharmacokinetic studies needs to be interpreted with caution as potential effects of decreased MPA exposure (when mycophenolate mofetil is given with PPIs or antacid medication) on efficacy endpoints, such as transplant rejection rates or graft loss, have not been studied.

Cholestyramine: Following single dose administration of 1.5 g mycophenolate mofetil to normal healthy subjects pretreated with 4 g three times daily of cholestyramine for 4 days, there was a mean 40% reduction in the AUC of MPA. This decrease is consistent with interruption of enterohepatic recirculation by irreversible binding, in the intestine, of recirculating MPAG with cholestyramine. Some degree of enterohepatic recirculation is also anticipated following IV administration of Mycophenolate Mofetil for Injection USP. Therefore, Mycophenolate Mofetil for Injection USP is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine: Mycophenolate mofetil has been investigated with Sandimmune® but not with the Neoral® formulation. Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 mg/day to 415 mg/day) were unaffected by single and multiple doses of 1.5 g twice daily of mycophenolate mofetil in ten stable renal transplant patients. The mean (±SD) AUC_{0-12} and C_{max} of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil. The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study; however, plasma concentrations of MPA were similar to that for healthy volunteers. Cyclosporine A (CsA) interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle (see WARNINGS AND PRECAUTIONS).

Drugs affecting glucuronidation

Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA AUC0-∞ by 35% was observed with concomitant administration of isavuconazole). Caution is therefore recommended when administering these drugs concomitantly with Mycophenolate Mofetil for Injection USP.

Ganciclovir: Following single-dose administration to twelve stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and IV 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 IV 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) mcg•h/mL and 30.9 (±11.2) mcg/mL, respectively after administration of mycophenolate mofetil alone. Therefore, no substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. However, because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the potential exists for the two drugs to compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which mycophenolate mofetil and ganciclovir or its prodrug e.g., valganciclovir are coadministrated, the dose recommendations for ganciclovir, or its prodrug e.g., valganciclovir should be observed and patients monitored carefully.

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

Tacrolimus: Exposure to tacrolimus concomitantly administered with mycophenolate mofetil had no effect on the AUC or C_{max} of MPA in hepatic transplant recipients. A similar finding was observed in a recent study in kidney transplant recipients.

In renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by mycophenolate mofetil.

However, in hepatic transplant patients, there was a 20% increase in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g twice daily) were administered to patients on tacrolimus.

Telmisartan: Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and glucuronidation. Experience with mycophenolate mofetil and telmisartan co-administration is limited. Caution should be exercised when Mycophenolate Mofetil for Injection USP is co-administered with telmisartan and monitoring of Mycophenolate Mofetil for Injection USP levels may be considered.

Oral contraceptives: Following single dose administration to healthy women, no pharmacokinetic interaction was observed between mycophenolate mofetil (1 g) and two tablets of Ortho-Novum® 7/7/7 (1 mg norethindrone [NET] and 35 mcg ethinyl estradiol [EE]).

Similarly, a study of coadministration of mycophenolate mofetil (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 mg - 0.04 mg) and levonorgestrel (0.05 mg - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg - 0.10 mg), conducted in 18 women with psoriasis over 3 menstrual cycles and showed no clinically relevant influence of mycophenolate mofetil on serum levels of progesterone, LH and FSH, thus indicating no influence of mycophenolate mofetil on the ovulation-suppressing action of the oral

contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of mycophenolate mofetil.

Although these studies demonstrate the lack of a gross pharmacokinetic interaction, one cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long term dosing conditions with mycophenolate mofetil which might adversely affect the efficacy of the oral contraceptive.

Antibiotics: antibiotics eliminating β-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure (see WARNINGS AND PRECAUTIONS).

Trimethoprim/sulfamethoxazole, norfloxacin and metronidazole: Following single dose administration of mycophenolate mofetil (1.5 g) to twelve healthy male volunteers on day 8 of a 10 day course of Bactrim® DS (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) mcg/mL, respectively compared to 79.2 (±27.9) mcg•h/mL and 34.2 (±10.7) mcg/mL, respectively after administration of mycophenolate mofetil alone.

No effect on the systemic exposure of MPA was observed when mycophenolate mofetil was concomitantly administered with any antibiotic separately. In contrast, the systemic exposure (AUC) of MPA was reduced by 10%, 19%, and 33% when mycophenolate mofetil was concomitantly administered with norfloxacin, metronidazole, and norfloxacin plus metronidazole, respectively, following a single dose of mycophenolate mofetil (statistically significant only for the differences seen in norfloxacin plus metronidazole when compared to baseline (P=.01)).

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

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

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

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

Concomitant administration of sevelamer and mycophenolate mofetil in adults and pediatric patients decreased the MPA C_{max} and AUC_{0-12} by 30% and 25 %, respectively. This data suggests that sevelamer or other calcium free phosphate binders should not be administered simultaneously with mycophenolate mofetil to minimize the impact on the absorption of MPA.

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

MMF is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. MMF did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

10.2 Pharmacodynamics

Refer to Section 10.1 Mechanism of Action. Additional information in the Product Monograph not included at the time of authorization.

10.3 Pharmacokinetics

Following oral and IV administration, MMF undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. The parent drug MMF can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 mcg/mL).

Absorption

In 12 healthy volunteers, the mean absolute bioavailability of oral MMF relative to IV MMF (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 MMF up to a daily dose of 3 g (see Table 5 below for pharmacokinetic parameters).

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 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 twelve healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥460 mcg/mL with plasma proteins) increased the free fraction of MPA. At concentrations exceeding those encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 mcg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism:
Following oral and intravenous dosing, MMF undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase (isoform UGT1A9) to form the phenolic glucuronide of MPA (MPAG).

In vivo, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia). 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.

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

Renal insufficiency has no consistent effect on MPA pharmacokinetics. Mean MPA AUC was increased by 50% in severe renal impairment (GFR <25 mL/min/1.73 m^2), however, there was considerable variation about the mean. For MPAG, there is an increase (3 - 6 fold) in mean AUC (see CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Insufficiency).

Elimination

Negligible amount of drug is excreted as MPA (<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 is not removed by hemodialysis. Similarly, MPAG concentrations normally encountered are unaffected by hemodialysis, however, at high MPAG plasma concentrations (>100 mcg/mL), small amounts of this metabolite are removed.

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 (±31) mL/min following IV administration, respectively.

MPA's disposition depends on several transporters. Organic anion transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

Special Populations and Conditions

- **Pediatrics**

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving mycophenolate mofetil oral suspension at a dose of 600 mg/m^2 twice daily (up to a maximum of 1 g twice daily) after allogeneic renal transplantation. This dose achieved MPA AUC values in pediatric patients

similar to those seen in adult renal transplant patients receiving mycophenolate mofetil capsules at a dose of 1g twice daily in the early post-transplant period. As observed in adults, early post-transplant MPA AUC values were approximately 45%-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 1-18 year age range.

- **Geriatrics**

Pharmacokinetics in the elderly has not been formally evaluated.

- **Sex**

Data obtained from several studies were pooled to examine any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC_{0-12} 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.

- **Pharmacokinetics in Healthy Volunteers, Renal, Cardiac and Hepatic Transplant Patients**

Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to healthy volunteers and multiple doses to renal, cardiac and hepatic transplant patients. In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late transplant period (3-6 months post-transplant). This is referred to as non-stationarity of MPA pharmacokinetics.

MPA AUC values obtained following administration of 1 g twice daily intravenous mycophenolate mofetil to renal transplant patients in the early post-transplant phase are comparable to those observed following 1 g twice daily oral mycophenolate mofetil. In hepatic transplant patients, administration of 1 g twice daily intravenous mycophenolate mofetil followed by 1.5 g twice daily oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil twice daily.

Table 5 Pharmacokinetic Parameters For MPA [mean (±SD)] Following Administration Of MMF To Healthy Volunteers (Single Dose), Renal, Cardiac And Hepatic Transplant Patients (Multiple Doses)

	Dose/Route	T_{max} (h)	C_{max} (mcg/mL)	Total AUC (mcg•h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (±0.36) (N=129)	24.5 (±9.5) (N=129)	63.9 (±16.2) (N=117)

Renal Transplant Patients (twice daily dosing) Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (mcg/mL)	Interdosing Interval AUC_{0-12} (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 (<40 days)	1 g /oral	1.31 (±0.76) (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 (±8.18) (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 (±35.4) (N=23)
Cardiac Transplant Patients (twice daily dosing) Time after Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC_{0-12} (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 (±20.8) (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 (twice daily dosing) Time after Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC_{0-12} (mcg•h/mL)**
4 - 9 days	1.0 g/iv	1.50 (±0.517) (N=22)	17.0 (±12.7) (N=22)	34.0 (±17.4) (N=22)
Early (5 - 8 days)	1.5 g/oral	1.15 (±0.432) (N=20)	13.1 (±6.76) (N=20)	29.2 (±11.9) (N=20)
Late (3 months)	1.5 g/oral	1.44 (±1.03) (N=9)	16.3 (±11.9) (N=9)	38.6 (±10.8) (N=9)
Late (> 6 months)	1.5 g/oral	1.37 (±0.477) (N=9)	19.6 (±9.86) (N=9)	52.5 (±14.4) (N=9)

* AUC_{0-12} values quoted are extrapolated from data from samples collected over 4 hours.

- **Delayed Renal Graft Function Post-Transplant**

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2-3 fold higher, compared to that seen in post-transplant patients without delayed renal graft function. In the three pivotal studies of prevention of rejection, 298 of 1,483 patients (20%) experienced delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia,

thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving mycophenolate mofetil than azathioprine or placebo. No dose adjustment is recommended for these patients, however, they should be carefully observed (see DOSAGE AND ADMINISTRATION: Dosage Adjustment, Delayed Renal Graft Function Post-Transplant).

- **Hemodialysis**

At clinically encountered concentrations, MPA is not removed by hemodialysis. Similarly, MPAG concentrations normally encountered are unaffected by hemodialysis, however, at high MPAG concentrations (>100 mcg/mL), hemodialysis removes only small amounts of MPAG.

- **Renal and Hepatic Insufficiency**

Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with renal and hepatic impairment.

Table 6 Pharmacokinetic Parameters for MPA [mean (±SD)] Following Single Doses of MMF Capsules in Chronic Renal and Hepatic Impairment

Renal Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (mcg/mL)	AUC_{0-96} (mcg•h/mL)
Healthy Volunteers GFR >80 mL/min/1.73m^2 (N=6)	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment GFR 50-80 mL/min/1.73m^2 (N=6)	1 g	0.75 (±0.27)	26.0 (±3.82)	59.9 (±12.9)
Moderate Renal Impairment GFR 25-49 mL/min/1.73m^2 (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR <25 mL/min/1.73m^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} (mcg/mL)**	**AUC_{0-48} (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)

- **Hepatic Insufficiency**

In a single dose (1 g, oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies may

show a different effect. In a single-dose (1 g) intravenous study of 6 volunteers with alcoholic cirrhosis, MPA AUC was 44.1 mcg•h/mL (±15.5).

- **Renal Insufficiency**

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

Plasma MPA AUC observed after single dose (1 g) intravenous dosing to volunteers (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) was 62.4 mcg•h/mL (±19.3). Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied (see DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment, Renal Impairment).

Subjects with severe chronic renal impairment who have received single doses of MMF showed higher mean plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy subjects. No data are available on the safety of long-term exposure to these levels of MPAG.

11 STORAGE AND STABILITY

Mycophenolate Mofetil for Injection USP: Store powder at 15ºC-30ºC.
Reconstituted/Further diluted (Infusion) solutions: Store at 15ºC-30ºC. Start treatment with reconstituted and further diluted, infusion solution within 4 hours.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

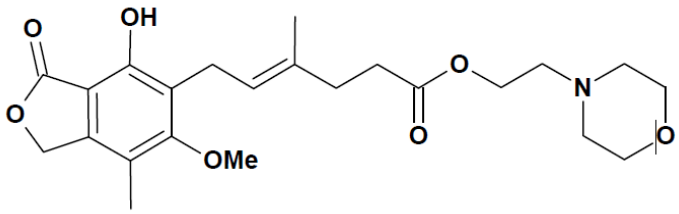
12 SPECIAL HANDLING INSTRUCTIONS

Mycophenolate mofetil has demonstrated teratogenic effects (see WARNINGS and PRECAUTIONS). Caution should be exercised in the handling and preparation of solutions of Mycophenolate Mofetil for Injection USP. Avoid skin contact of the solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Should a spill occur, wipe up using paper towels wetted with water to remove spilled powder. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	Mycophenolate Mofetil
Chemical Name	2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate
Molecular Formula and molecular mass	$C_{23}H_{31}NO_7$, 433.50
Structural Formula	
Physiochemical properties	Mycophenolate mofetil is a white or almost white, crystalline powder.

Product Characteristics:

Solubility	Freely soluble in acetone, soluble in methanol, sparingly soluble in dehydrated alcohol and slightly soluble in water.
pKa Values	pKa_1 = 5.6 for morpholino functional group pKa_2 = 8.5 for phenolic functional group
Partition Co-efficient	The apparent partition co-efficient in 1-octanol/water buffer solution (pH 7.4) is 238.
Melting point	Between 95.5°C and 98.0°C

The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E) 6-(1, 3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7$ HCl and a molecular weight of 469.96. Mycophenolate mofetil hydrochloride salt is formed in-situ and has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The safety and efficacy of mycophenolate mofetil as adjunctive therapy for the prevention of organ rejection were assessed in randomized, double-blind, multicentre trials in renal (3 trials), in cardiac (1 trial) and in hepatic (1 trial) transplant patients.

Renal Transplant

Adult

The three renal studies 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 and corticosteroids to prevent acute rejection episodes. One study also included anti-thymocyte globulin [equine] (Atgam®) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the US at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced biopsy-proven acute rejection or treatment failure (defined as early termination from the study for any reason without prior biopsy-proven rejection) within the first six months after transplantation. Mycophenolate mofetil, when administered with anti-thymocyte globulin [equine] (Atgam®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was shown to significantly reduce the incidence of treatment failure compared to the following three therapeutic regimens: (1) anti-thymocyte globulin [equine] (Atgam®) induction/ azathioprine/ cyclosporine/corticosteroids, (2) azathioprine/ cyclosporine /corticosteroids, and (3) cyclosporine/corticosteroids.

Pediatrics

One open-label, safety and pharmacokinetic study of mycophenolate mofetil oral suspension 600 mg/m^2 twice daily (up to 1g twice daily) 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.

Cardiac Transplant

A double-blind, randomized, comparative, parallel-group, multicentre study in primary cardiac transplant recipients was performed at 20 centers in the United States, one in Canada, five in Europe and two in Australia. The total number of patients enrolled was 650; 72 patients did not receive study drug and 578 patients received study drug. Patients received mycophenolate mofetil 1.5g twice daily (n=289) or azathioprine 1.5-3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune® or Neoral®) and corticosteroids as maintenance immunosuppressive therapy.

Hepatic Transplant

A double-blind, randomized, comparative, parallel-group, multicentre study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565. Patients received mycophenolate mofetil 1g twice daily intravenously for up to 14 days followed by mycophenolate mofetil 1.5 g twice daily orally or azathioprine 1-2 mg/kg/day intravenously followed by azathioprine 1-2 mg/kg/day orally, in combination with cyclosporine (Neoral®) and corticosteroids as maintenance immunosuppressive therapy.

14.2 Study Results

Renal Transplant

Adult

Mycophenolate mofetil, in combination with corticosteroids and cyclosporine reduced (statistically significant at the <0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables 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 discontinued receiving mycophenolate mofetil (without prior biopsy-proven rejection, death or graft loss) than discontinued in the control groups, with the highest rate in the mycophenolate mofetil 3 g/day group. Therefore, the acute rejection rates may be underestimated, particularly in the mycophenolate mofetil 3 g/day group.

Table 7 Renal Transplant Studies - Incidence of Treatment Failure (Biopsy-Proven Rejection or Early Termination for Any Reason)

USA Study (N=499 patients)	MMF 2 g/day (N=167 patients)	MMF 3 g/day (N=166 patients)	Azathioprine 1-2 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=503 patients)	MMF 2 g/day (N=173 patients)	MMF 3 g/day (N=164 patients)	Azathioprine 100-150 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)	MMF 2 g/day (N=165 patients)	MMF 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%

* Does not include death and graft loss as reason for early termination.

Cumulative incidence of 12-month graft loss and patient death are presented below. No advantage of mycophenolate mofetil with respect to graft loss and 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 and patient death at 1 year.

Table 8 Renal Transplant Studies
Cumulative Incidence of Combined Graft Loss and Patient Death at 12 Months

Study	MMF 2 g/day	MMF 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

Mycophenolate mofetil was well tolerated in pediatric patients (see ADVERSE REACTIONS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1g twice daily mycophenolate mofetil capsules (see CLINICAL PHARMACOLOGY: Special Populations and Conditions, Pediatrics). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 to <12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss and patient death at 12 months post-transplant were similar to the rates observed in adult renal transplant patients.

Cardiac Transplant

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 six months, and (2) the proportion of patients who died or were transplanted during the first twelve months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

(1) Rejection: No difference was established between mycophenolate mofetil and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise.

(2) Survival: mycophenolate mofetil was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year (see table below).

Table 9 Cardiac Transplant Study - Rejection at 6 Months Death or Retransplantation at 1 Year

	All Patients		Treated Patients	
	AZA N = 323	MMF N = 327	AZA N = 289	MMF N = 289
Biopsy-proven rejection with hemodynamic compromise at6 months*	121 (38%)	120 (37%)	100 (35%)	92 (32%)
Death or Retransplantation at1 year	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

* Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥ 20 mmHg or a 25% increase; cardiac index < 2.0 L/min/m^2 or a 25% decrease; ejection fraction ≤ 30%; pulmonary artery oxygen

saturation <60% or a 25% decrease; presence of new S_3 gallop; fractional shortening was ≤ 20% or a 25% decrease; inotropic support required to manage the clinical condition.

Hepatic Transplant

The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months post-transplantation, one or more episodes of biopsy-proven and treated rejection or death/retransplantation, and (2) the proportion of patients who experienced graft loss (death/retransplantation) during the first 12 months posttransplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/retransplantation) for 1 year. Results: In the primary (intent-to-treat) analyses mycophenolate mofetil in combination with corticosteroids and cyclosporine was statistically significant ($p < 0.02$) compared to azathioprine for prevention of acute rejection and equivalent to azathioprine for survival.

Table 10 Hepatic Transplant Study - Rejection at 6 Months / Death or Retransplantation at 1 Year

	AZA N = 287	MMF N = 278
Biopsy-proven and treated rejection at 6 months	137 (47.7%)	106 (38.1%)
Death or retransplantation at 1 year	42 (14.6%)	39 (14.0%)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Animal Pharmacology

Survival of Allografts and Treatment of Allograft Rejection in Different Experimental Models

The effect of MMF for the prevention of rejection and for the reversion of ongoing rejection was studied in several experimental allograft models.

Survival of Kidney Allografts and Treatment of Acute Allograft Rejection in Dogs

To determine the efficacy of MMF in preventing graft rejection in a large animal model, a renal allograft between outbred mongrel dogs was used. In control dogs receiving no immunosuppression, the median graft survival (MST) was 8.1 days. MMF administered orally at 40 mg/kg/day significantly increased the allograft survival (MST = 36 days). Some gastrointestinal toxicity and weight loss was observed in this group of dogs. When MMF (20 mg/kg/day) was given in combination with subtherapeutic doses of cyclosporin A (CsA, 5 mg/kg/day) and methylprednisolone (MP, 0.1 mg/kg/day), the MST was >122.4 days (n=16). Using this triple therapy, three dogs survived >200 days and one was euthanized on Day 150 to obtain tissue samples for histologic examination. In the animals treated with triple therapy, no significant toxicity was observed. There was a two-fold transient increase in alkaline phosphatase. Control dogs treated with CsA (5 mg/kg/day) and MP (0.1 mg/kg/day) had a MST = 8.5, essentially identical to that in untreated dogs. In dogs receiving 20 mg/kg/day MMF and 0.1 mg/kg/day MP without CsA, all animals survived >50 days (n=6). The treatment was discontinued in 4 of those animals to test for tolerance after 50 days. Within a few days those 4 animals underwent acute renal rejection, indicating that tolerance had not developed. Nonetheless, the double therapy treatment without CsA was as effective at preventing rejection as was the therapy with CsA.

The ability of MMF to reverse ongoing acute rejection was also examined in the canine renal allograft model. Kidney allografts were performed in bilaterally nephrectomized female mongrel dogs. All animals received a baseline immunosuppressive treatment (MMF - 10 mg, CsA - 5 mg and MP - 0.1 mg/kg/day, orally), previously shown to be insufficient to prevent renal graft rejection, but sufficient to slow the rate of progression. Rejection was defined by a 50% or greater rise in serum creatinine level relative to the lowest observed creatinine during the first postoperative week. Before the initiation of rejection treatment, a percutaneous kidney biopsy was performed to confirm the rejection. At the time of rejection, experimental animals received rescue therapy consisting of either MMF 80 mg/kg/day, twice daily, for 3 days, (experimental group) or bolus MP: 14 mg/kg, 7 mg/kg and 3.5 mg/kg, respectively, on each day (control group). After completion of the rejection treatment, the baseline immunosuppression was increased to MMF 20 mg/kg, with the same doses of CsA and MP.

Control animals (n=11) all died of ongoing rejection (MST 19 days). In the experimental group, MMF treatment successfully reversed the acute ongoing rejection in 14/16 (87.5%) of the dogs. Reversion of the rejection process was proven by biopsy as well as normalization of the creatinine levels. The rejection treatment with MMF resulted in a lymphopenia that persisted for about 4 weeks, while liver enzymes such as AST, ALT and alkaline phosphatase were minimally elevated during the first two weeks after rejection treatment. During the rescue

therapy with MMF, gastrointestinal side effects such as vomiting and diarrhea were also observed.

In summary, MMF significantly prolonged kidney allograft survival in dogs. Using a combined treatment with subtherapeutic doses of CsA and MP, the graft survival was >122 days, without any serious adverse effects. In addition, MMF was highly effective in reversing acute renal allograft rejection in dogs, while bolus administration of steroids did not show efficacy in the same model. These studies show the efficacy of MMF in preventing and treating allograft rejection without limiting toxicity or increased susceptibility to infections in a large animal model.

Prevention of Acute Rejection in Heart Allografts and Xenografts in Mice and Rats
MMF was found to effectively prolong heart allograft survival in mice and rats, and increase xenograft survival and reverse ongoing allograft rejection without severe toxicity in rats. The survival of grafts long beyond cessation of treatment, and even after challenge with a second graft from the same donor, suggested induction of tolerance. Combination therapy with MMF and CsA, using low doses of both drugs, can prevent graft rejection and allow survival even after cessation of treatment. Thus CsA and MMF have at least additive effects in preventing allograft rejection, without indication of increased toxicity. Similarly, MMF and brequinar also demonstrated an additive effect on preventing heart allograft rejection in rats, without increased toxicity.

Prevention of Chronic Rejection in Heart Allografts and Aortic Allografts in Rats
A manifestation of chronic allograft rejection is a proliferative and obliterative arteriopathy. MPA in clinically attainable concentrations (0.09-3.2 µM) inhibits the proliferation of human arterial smooth muscle cells in culture, whereas CsA and brequinar do not. Once daily oral administration of MMF (30 mg/kg/day, Days 1-30 and 20 mg/kg/day, Days 31-100) to Lewis rat recipients prevented the development of chronic rejection in transplanted Brown Norway rat heart allografts.

Male ACI rat donors and Lewis recipient rats were used in an orthotopic aortic allograft model to test the effect of MMF in preventing development of chronic rejection. Treatment with a MMF dose (20 mg/kg) for 3 months significantly inhibited intimal proliferation when used alone and in combination therapy with brequinar sodium. By contrast, brequinar monotherapy and CsA alone did not prevent neointimal proliferation at the doses used. MMF was also tested at lower doses with other immunosuppressive regimens containing rapamycin and was found to be partially active.

Survival of Cardiac Xenografts in Primates

Cynomolgus monkeys served as donors for ABO-matched, B-cell-crossmatched negative, baboons. Four treatment groups were used: Group 1, no immunosuppression; Group 2, CsA 15 mg/kg/day intramuscularly starting 1 day preoperatively + methylprednisolone acetate 0.8 mg/kg/day intramuscularly; Group 3, same as Group 2 + azathioprine 4 mg/kg/day orally starting 21 days preoperatively; Group 4, same as Group 3 with MMF 70 mg/kg/day orally instead of azathioprine.

Group 1 baboons (n = 4, untreated controls) had a MST of 9 days (range 8-10 days). CsA and steroid treatment in Group 2 (n = 6) prolonged mean survival to 77 days (range 16-200 days). Hearts undergoing early rejection showed a histologic picture of rejection similar to that of Group 1. Hearts with longer survival demonstrated histological appearance consistent with repeated episodes of rejection, with healing and gradual replacement of myocardium with connective tissue. Graft biopsy was performed at 1, 2, 4, 8 and 12 weeks post operatively in groups 3 and 4 with follow-up biopsy 1 week after rejection therapy. In Group 3 (n = 5), mean survival was prolonged to 94 days (range 3-392). Four of 9 rejection episodes were reversed using high-dose steroids. ATG 10 mg/kg per day intravenously reversed 2 of 4 episodes of steroid-resistant rejection. Despite rescue from cellular rejection, these grafts were later lost to humoral rejection. In Group 4 (n = 3), mean survival was 296 days (range 49-618). A cardiac biopsy taken from 1 animal in group 4 at 618 days post-transplant showed a coronary artery free of intimal occlusive disease. Coronary artery disease of a low degree of severity was found in only 2 other biopsy specimens in group 4 and consisted of moderate endothelial swelling. There was no evidence of coronary intimal proliferation in this group.

Ultrastructural examination of the coronary arteries and veins from the same animal showed no indication of vasculopathy in any of the vessels examined. The endothelium in some vessels was bulbous in appearance rather than the normal flat endothelial lining.

In conclusion, MMF in combination with a subtherapeutic dose of CsA and steroids significantly prolonged cardiac xenograft survival in primates far beyond any other immunosuppressive regime so far tested. The vascular pathological changes seen in long-term survivors with cardiac xenografts treated with other immunosuppressive therapies were not observed in animals treated with MMF.

In addition, MMF significantly inhibited neointimal proliferation in rat aortic allografts after 6 months treatment, while CsA and brequinar did not. MMF also prevented the intimal proliferation observed in long-term recipients of rat heart allografts, while CsA and azathioprine did not. This effect may be explained by the ability of MMF to inhibit not only T-lymphocyte

responses, but also antibody formation and proliferation of smooth muscle cells, which are considered important factors contributing to the pathogenesis of chronic rejection.

Other Models of Allograft Rejection

MMF (80 mg/kg/day) was effective for prevention of pancreatic islet allograft rejection in mice rendered diabetic using streptozotocin. After cessation of treatment, recipients of pancreatic islet allografts continued normoglycemic, indicating that a state of tolerance was induced. Tolerant mice resisted challenge with a second graft from the same donor strain but rejected a third party graft, indicating that the tolerance induced by MMF was specific. In animals (NOD mice) spontaneously developing diabetes, MMF (80 mg/kg/day) did not decrease the incidence of disease.

MMF was also effective in graft versus host disease (GVHD) in several experimental models using splenocytes from parental C57Bl/6 mice into F_1 (C57Bl/6 x C3H/H3N) mice, rat small bowl transplant from parental into F_1 recipients, and a sublethally irradiated mouse recipient of allogenic spleen cells model. In other models of allograft rejection such as limb transplants in rats and liver and intestinal allograft in dogs and rats, MMF alone and in combination with CsA showed increased survival and greater efficacy than other immunosuppressive therapies tested in parallel.

Mechanism of Action

Immunosuppressive Effects

In vitro Studies with Human Cells

The effects of MMF and MPA on lymphocyte function were studied in vitro. MPA and MMF (IC_{50}=17-80 nM) inhibit proliferative responses of human peripheral blood mononuclear cells (PBMCs) to the T- and B-cell mitogens phytohemagglutinin (PHA), pokeweed mitogen (PWM), concanavalin A (Con A) and Staphylococcus protein A-sepharose (SPAS). By contrast MPAG was not inhibitory of lymphocyte proliferation in response to PWM and SPAS up to 10 µM concentration. Lymphocyte response to phytohemagglatin PHA was inhibited by MPAG with an IC_{50}=8.9µM. This concentration is about 100-fold greater than the MPA concentration required for the same bioactivity. The residual activity in the MPAG sample can be explained by a small contamination with MPA as detected by HPLC analysis (≈0.3%).

Addition of guanosine (Guo) or deoxyguanosine (dGuo) reversed the inhibitory effect of MMF and MPA, while adenosine and deoxyadenosine had no effect. Human fibroblasts, endothelial cells, and smooth muscle cells were about one log less sensitive to the antiproliferative effects of the drug than were lymphocytes.

In addition, MMF and MPA inhibited the formation of antibodies by human peripheral blood B-lymphocytes stimulated with mitogens (*Staphylococcus aureus* Cowan 1 or PWM) at nanomolar concentrations (IC_{50} of approximately 20-50 nM).

Measurements of nucleotide pools in human lymphocytes activated with concanavalin A (Con A), as well as in the human T-cell line CCRF-CEM, have shown that MPA (1 µM) markedly depletes pools of GTP. When either Guo (1 µM) or dGuo (10 µM) were added to the medium, the GTP level was restored. The dGTP pools were even more affected by MPA than those of GTP, and dGuo (10 µM) restored the level to above the controls. By contrast, GTP levels in human polymorphonuclear leukocytes (PMNs) were essentially unaffected by MPA, while adherent mononuclear cells (monocyte-enriched) were also GTP depleted. The effect of MPA was greater in mononuclear cells stimulated by Con A than on resting cells.

MMF and MPA were also shown to be potent inhibitors of the proliferation of human B- and T-lymphocytic and promonocytic cell lines, while the erythroid precursor cell line, K562, was less susceptible. Several human tumor cell were found to have various degrees of susceptibility to the antiproliferative effects of MMF and MPA. Addition of guanine or dGuo to the cultures reversed the antiproliferative effect of MPA in a concentration- and time-dependent manner, showing the selectivity of the drug's effect.

The observation that MPA added to mixed lymphocyte cultures after 72 hours still inhibited proliferation suggests that the drug affects late events following antigenic stimulation. MMF and MPA did not inhibit early events in lymphocyte activation, such as production of IL-1 by human peripheral blood monocytes stimulated with lipopolysaccharide, the production of IL-2 in Con A stimulated human peripheral blood lymphocyte (PBL) and the mobilization of calcium following stimulation of T-cells with mitogens.

Interferon (IFN-γ) is another cytokine produced by stimulated T-lymphocytes. MMF (hydrochloride) did not inhibit IFN production in 2 assays. Subsequently, MMF was found to inhibit IFN production with an IC_{50} of 0.37-0.42 µM, which is about 10-fold greater than the concentration required to inhibit lymphocyte proliferation.

Although inhibition of T- and B-lymphocyte proliferation is the primary target of the drug, it is likely that depletion of GTP will have other metabolic effects on these cells. For example, it is known that GTP is required for the activation of mannose and fucose, through dolichol phosphate intermediates, for glycoprotein (and glycolipid) biosynthesis. Fucose-containing oligosaccharides are components of adhesion molecules such as ligands for selections which

are expressed on activated endothelial cells, lymphocytes and monocytes and facilitate their interactions at sites of inflammation and graft rejection.

Cultures of human umbilical vein endothelial cells (HUVEC) and a human T-lymphocytic cell line (CEM) were used to evaluate the effect of MPA on cell adhesion. When the HUVEC were stimulated with cytokines such as IL-1 or TNF, there was a dose-dependent increase in the number of lymphocytic cells adhering to the endothelial cells (EC). The number of lymphocytes attached to the cultured EC was measured by counting under the microscope or using ^{51}Cr-labelled T-cells. When the T-cells were treated for 4 hr with 1 µM MPA prior to incubation with EC, a reduction in the number of adherent cells was observed. Treatment of both, the EC and the T-cells with MPA (10 µM) for the same time, markedly decreased the attachment between the two cell types. This observation suggests that MPA prevents the glycosylation of adhesion molecules on lymphocytes and EC. Similar results have been obtained using human PBL stimulated with Con A instead of a T-cell line.

Immunoprecipitation studies using monoclonal antibodies specific for the adhesion molecules, VLA-4 and LFA-1, showed that MPA (10 µM) inhibited the incorporation of sugars (^{3}H- mannose and ^{3}H-glucosamine) on the surface of PHA-activated human PBM. By flow-cytometry, MPA was also shown to inhibit the binding by PHA activated PBM of specific lectins that recognize terminal mannose residues and sialic acid attached to terminal galactose.

In summary, MPA in clinically attainable doses can inhibit the binding of mononuclear cells to endothelial cells. This mechanism could contribute to the efficacy of MMF in preventing allograft rejection and in the treatment of ongoing rejection when clones of lymphocytes with specificity for alloantigens have already expanded.

MPA inhibited the proliferation of human arterial smooth muscle cells (SMC) and endothelial cells (HUVEC) with IC_{50}s between 0.09-3.2 µM.

In another study, MPA was tested for effects on the growth of arterial smooth muscle cells. Human iliac artery smooth muscle cells were obtained from medial explants and were passaged several times before use. MPA was inactive at low doses, but showed 30% inhibition of cell proliferation at a concentration of 1.6 µM. MPA was also studied using human breast carcinoma cell lines BT20 and MCF-7 in comparison with non-transformed human foreskin fibroblasts. MPA at concentrations between 5-50 µM inhibited the growth of both the breast carcinoma lines and the human foreskin fibroblasts (HFF) by 50%. The sensitivity of the breast cancer cell lines to the antiproliferative effect of MPA was not significantly different from the HFF.

MMF and MPA at submicromolar concentration also inhibited proliferation and induced differentiation of promonocytic cells (U-937, HL-60 and THP-1), as measured by increased expression of cell surface markers, increased secretion of lysozyme and raised intracellular concentrations of lysosomal enzymes. U-937 and THP-1 cells cultured for 72 hr with 1 µM MPA had an increased lipid droplet content as determined by fluorescence microscopy and transmission electron microscopy. MPA also induced human derived macrophages to produce lysosomal hydrolases, supernatant lysozyme and the interleukin-1 receptor antagonist protein (IL-1ra). These effects are characteristic of compounds having long-acting anti-inflammatory effects (DMARDs) such as chloroquine and gold salts which suggests that MMF could have a disease-modifying effect in chronic inflammatory conditions such as rheumatoid arthritis.

In vitro Studies with Cells from Laboratory Animals

MPA was tested in vitro at concentrations of 0.001 to 10 µM for inhibition of lymphocyte proliferation in cell cultures from rhesus monkey, rabbit, guinea pig, rat and mice. The mitogens used were PHA, PWM, Con A, SPAS and bacterial lipopolysaccharide (LPS). MPA inhibited lymphocyte proliferation to all of the mitogens in lymphocyte cultures from all of the above named species with IC_{50}s between <1-60 nM.

Mixed lymphocyte reactions were initiated using C57Bl/6J mouse splenocytes as responder cells and BALB/cJ mouse splenocytes as stimulator cells. After 4 days incubation in the presence of MPA at various concentrations, cell proliferation was determined by ^{3}H-thymidine incorporation and cell viability was determined by trypan blue dye exclusion. The IC_{50} for MPA was determined to be 0.4 µM; cell viability was reduced at MPA concentrations ≥ 0.3 µM.

The effects of MPA on murine in vitro antibody-forming cells were analysed in a series of studies. In 1 study, MPA suppressed the in vitro response to sheep red blood cells (SRBC) >85% at concentrations of 0.1 or 1.0 µM. In this same study, a dose-response curve gave an estimated IC_{50} of approximately 0.04 µM. In a second study with mouse spleen cells stimulated with SRBC, only the 1.0 µM dose was suppressive and the dose-response curve showed significant suppression beginning at 50 nM. In the last study, murine spleen cells and peritoneal lymphocytes were stimulated in culture with LPS and evaluated for the production of autoantibodies to murine red blood cell antigens pretreated with bromelain. Both splenic and peritoneal B-cells showed variability in response to MPA. Peritoneal cell IC_{50} ranged from 0.27 µM to >10 µM, whereas spleen cell IC_{50} ranged from 0.59 µM to >100 µM.

The effect of MPA on the effector phase of NK-cell activity in mice was also assessed at MPA concentrations of 1, 10 and 100 µM using YAC-1 tumor cells as targets. Only at the 100 µM

concentration did MPA inhibit the effector phase of NK-cell activity in 2 of 3 experiments. MPA tested on the effector phase of T-cell-mediated cytotoxicity in a murine system (spleen cells sensitized to P815 tumor target cells) was only partially inhibitory (30% decrease in specific lysis) at the highest concentration tested (100 µM) in 1 of 2 experiments.

The effect of MPA on the degranulation of rat peritoneal mast cells (RMC) was studied. RMC were pretreated for 48 hr with 0.1-10 µM MPA before the cells were sensitized with IgE and triggered with specific antigen. The net amount of ^{3}H-5HT released from granules was decreased by 44 and 32% at 1 and 10 µM, respectively. MPA inhibition of degranulation was completely reversed by the addition of 30 µM guanosine to the medium. MPA had no effect on any other cell parameters studied (IgE receptors or PGD2 production).

In vivo Studies in Experimental Animals

The effects of MMF and MPA on antibody formation were tested using SRBC to immunize mice and rats. Significant inhibition (40%-88%) of the antibody response was observed in mice with oral doses of 20-100 mg/kg/day of MMF or MPA administered once daily for 4 days. In rats immunized with SRBC and treated with MPA for 4 days only, the ED_{50} was approximately 14 mg/kg/day. Significant inhibition of antibody formation against SRBC was observed also in rats treated with 9 and 30 mg/kg/day for 28 days, and immunized 4 days before the end of treatment.

MPAG, the main metabolite of MPA, was also tested for activity on antibody production in mice immunized with SRBC. MPAG given orally for 4 days at 50 mg/kg/day, significantly inhibited the total number of antibody-forming cells in the spleen (PFC) by 60%. These results show that MPAG, which *in vitro* is >100-fold less active than MPA on lymphocyte proliferation, has comparable *in vivo* activity. These results are consistent with the observations that *in vivo*, MPAG is converted to free MPA, probably by enterohepatic recirculation, with bioactivity comparable to that induced by MPA administration.

Primary and secondary antibody responses were analyzed in mice immunized with B/Yamagata influenza virus hemagglutinin in adjuvant. MPA given orally (80 mg/kg) from the time of primary immunization, for 10 days, significantly reduced the antibody titers after primary immunization and also after challenge, even though no additional drug treatment was given. Moreover, if no treatment was given at the time of primary immunization, but only after challenge, the antibody response was not reduced. These observations indicate that MPA effectively suppresses antibody responses if administered during immunization but is less effective after sensitization has already occurred.

Oral administration of MMF and MPA (50-120 mg/kg/day) from day 1 to 11 to C57Bl/6 mice also suppresses the generation of cytotoxic T-lymphocytes able to lyse allogeneic tumor target cells (P-815 mastocytoma) given intraperitoneally (day 1). Cytotoxic T-cells are thought to be the main effector mechanism responsible for acute allograft rejection. The efficacy of MMF and MPA in preventing cytotoxic cell generation provides the rationale for the prophylactic use of this drug to prevent rejection in allograft recipients.

MPA administered orally or intraperitoneally (100 mg/kg, 3-5 days) to mice immunized with ovalbumin was found to inhibit the synthesis of DNA as measured by ^{3}H-TdR incorporation in lymphoid tissue but not in other rapidly dividing cells such as germinal cells of the testes. Thus MPA has a more potent cytostatic effect on lymphoid cells than in other cell types, in vivo as well as in vitro.

Anti-Inflammatory Effects

MMF and MPA were tested in a number of experimental models of inflammation. Both MMF and MPA suppress adjuvant-induced arthritis and experimental allergic encephalomyelitis in rats.

The autoimmune disease that develops in genetically predisposed MRL/pr mice was also partially reduced by treatment with MPA for 30 days, starting at 5.5 months of age. In collagen-induced arthritis in mice, MPA did not produce any significant changes of the disease symptoms or incidence at the dose tested (10.5 mg/kg/day). However, this dose was considered to be below the threshold of therapeutic activity in mice, as shown in other models.

No effect was observed when MPA was administered to rats in two other models of acute inflammation, carrageenan-induced paw swelling and granuloma induced by implant of a cotton-pellet impregnated with carrageenan.

Finally, MPA was found to have no effect on IL-1-induced ornithine decarboxylase in mice (used as a measure of an acute phase response).

As part of a random screening, MPA was tested in vitro for inhibition of 15-lipoxygenase and 5 lipoxygenase (5-LO) activity, and for thromboxane B_2 and leukotriene B_4 (LTB_4) synthesis by human whole blood. A partial inhibitory effect on LTB4 synthesis and 5-LO activity was found only at the highest concentrations tested (312 and 100 µM, respectively).

These results indicate that MMF and MPA can prevent inflammatory responses that are immunologically driven but have no effect on acute inflammatory responses such as those responding to cyclo-oxygenase and 5-LO inhibitors.

Antitumor Effects

Antitumor activity of MMF was assessed in several models of xenogeneic (human tumor cells into nude mice) as well as in a syngeneic metastasis model in mice. MMF significantly prolonged survival and delayed tumor development with different degrees of efficacy according to the type of tumor.

Antiviral Effects

Antiviral activity of MMF and MPA was evaluated against different viruses in culture. Anti-HIV activity was tested using different cell lines of T-cell and monocytic origin. In general, the reduction in reverse transcriptase (RT) was directly correlated with the reduction in the cell number, suggesting that the effect of MPA is at the cellular level rather than on the virus replication. Antiviral activity against herpes, parainfluenza virus, respiratory syncitial virus and against murine Friend Leukemia Virus (FLV) were all obtained at low (micromolar) concentrations of MPA, but the window between antiviral concentration and cytostatic effects was narrow. *In vivo*, MMF and MPA inhibited splenomegaly and the number of focus forming units in FLV-infected mice. Some activity of MMF and MPA against cytomegalovirus and human cytomegalovirus was observed; these drugs augmented the antiviral activity of ganciclovir.

General Pharmacology

General pharmacology studies were conducted to assess the effects of MMF on the central nervous, cardiovascular, respiratory, and gastrointestinal systems.

CNS effects were determined in mice in studies that included a gross behavioral assay (Irwin Profile), a spontaneous locomotor activity assay, an induced neurological deficit test, maximal electroshock and pentylenetetrazol anticonvulsant assays, and a hexobarbital sleep test. MMF was administered as single oral doses ranging from 1.09 to 1090 mg/kg. Except for depressed locomotor function at 10.9 mg/kg and higher doses in the Irwin profile assay or at 109 mg/kg in the spontaneous locomotor activity assay, there was no evidence of central nervous system or autonomic effects with MMF.

Cardiovascular and respiratory effects were assessed in anesthetized dogs, 3 animals per group. Each animal received escalating doses of MMF (0.3-31.6 mg/kg, orally). No significant effects were seen.

Effects on gastrointestinal function were determined in rats, 5-10 animals per group. Each rat received single oral doses of MMF (25-100 mg/kg). MMF significantly decreased gastrointestinal motility at 100 mg/kg, but had no effects on gastric secretory activity. MMF appeared to diminish signs of colitis in a mouse model; however, this model was unverified and the results are inconclusive.

To further assess the affinity of MMF and MPA at various neurotransmitter receptors, radioligand binding assays were performed. Both MMF and MPA showed low affinities (pK_i values ≤ 4-5) at α-adrenergic, β-adrenergic, and muscarinic receptors, suggesting probable lack of activity for these compounds on the autonomic nervous system.

Pharmacokinetics and Disposition

MMF administered orally to animals and humans was rapidly and extensively converted to MPA. Following oral administration of unlabeled MMF or [^{14}C-MPA] MMF to mice (10 mg/kg), rats (6 mg/kg), rabbits (40 mg/kg), dogs (9 mg/kg), mini pigs (45 mg/kg), cynomolgus monkeys (6 mg/kg), and humans (1000 mg), MMF was not detected in plasma by HPLC-UV or HPLC-radiometric methods. Following IV infusion of MMF, however, MMF was observed in the plasma throughout the infusion period but was not detected >5 minutes after terminating the infusion. Subsequent in vitro studies using monkey and human tissues demonstrated that homogenates of liver, gut mucosa, and kidney hydrolyze MMF to MPA and hydroxyethyl morpholine.

Pharmacokinetic-based Drug Interactions

Co-administration of MMF (20 mg/kg orally) and probenecid (500 mg) twice daily for 4 days increased the $AUC_{0\text{-}12\ hr}$ for MPA and MPAG 1.7 and 2.9 fold respectively.

The potential for drug interaction at the level of protein binding was evaluated in human plasma *in vitro* by equilibrium dialysis and ultrafiltration methods. When MPA concentrations of 5, 20, and 50 mcg/mL were used, concentrations of MPAG as high as 230 mcg/mL had little effect on the binding of MPA. However, MPAG concentrations of 460 and 920 mcg/mL reduced the plasma binding of MPA (50 mcg/mL) from 97.1% to 95.4% and 92.8%, respectively. At plasma concentrations encountered clinically, tolbutamide, theophylline, and digoxin had no effect on the binding of MPA to human plasma, but cyclosporine at 500 ng/mL reduced the binding of MPA (75 mcg/mL) from 97.2% to 96.5%. MPA concentrations as high as 100 mcg/mL had little effect on the plasma binding of warfarin, digoxin, or proprandol, but decreased binding of theophylline from 52.8% to 45.0%, and decreased binding of phenytoin from 90.0% to 86.8%.

Miscellaneous Studies

The potential for MMF to induce hepatic cytochrome P450 enzymes was evaluated in male rats. MMF did not induce total hepatic P_{450}.

Glucuronidation of MPA by Hepatic Microsomes

Apparent K_m and V_{max} of glucuronidation of MPA were determined with hepatic microsomes from mice, rats, dogs, cynomolgus monkeys, and humans (CL 6755). Microsomes from all species catalyzed the formation of MPAG from MPA, and the reaction followed Michaelis-Menton kinetics.

Nonclinical toxicity studies were conducted to evaluate the acute, subchronic/chronic, reproductive, carcinogenic, and mutagenic effects of MMF.

Clinically MMF will be administered orally as a capsule. Therefore, the primary route of exposure for the toxicology studies was oral (gavage). Oral bioavailability of MPA following MMF administration, and absorption efficiency of MMF, were known to range from approximately 80% to 100% in rodents (mice, rats) to 50% to 70% in non-rodents (dogs, monkeys). Additional toxicology studies were conducted by the intravenous and subcutaneous routes to further characterize MMF's toxicologic profile.

Animal models used in toxicology evaluations included mice, rats, dogs (beagle), and monkeys (cynomolgus), and were selected in part for their known pharmacological responsiveness to MMF and similar metabolism of MMF compared with man.

Single-dose (Acute) Toxicity

The acute toxicity of MMF was evaluated by oral, subcutaneous, and intravenous routes in mice, rats, and/or monkey.

Table 11 Single Dose (Acute) Toxicity Studies

Document No.	Study Type	Species	Dose (mg/kg)	Route
Oral Toxicology Formulation:				
AT 4107	Acute	Mouse	500-4000	Oral
AT 4108	Acute	Rat	125-1000	Oral
AT 4109	Acute	Rat	250-2000	Subcutaneous
AT 4099	Acute	Monkey	500-1000	Oral
Intravenous Toxicology Formulation:				
AT 5996	Acute	Rat	10-100	Intravenous

Single acute minimum lethal oral doses were greater than 4000 mg/kg in mice, 250 mg/kg in rats, and 1000 mg/kg in monkeys. The acute minimum lethal dose in rats was greater than 1000 mg/kg by the subcutaneous route. In these oral and subcutaneous acute toxicity studies, treatment-related mortality occurred only in the rat. Most deaths occurred 3 to 6 days after dosing and were associated with gastrointestinal toxicity, evidenced pathologically by excess fluid, mucosal reddening, and/or ulceration in the stomach and/or small intestine.

The acute minimum lethal dose in rats was between 30 and 100 mg/kg by the intravenous route. Most rats died within 2 minutes after dosing. Clinical changes at 30 and 100 mg/kg included collapse, inactivity, tonic convulsion, labored respiration, and/or gasping; these changes abated by 3 hours postdosing. No treatment-related pathologic changes occurred.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 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 body surface area (BSA). In adult rats, deaths occurred after single oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents 3 times the recommended clinical dose in renal transplant patients and approximately twice the recommended clinical dose in cardiac transplant patients when corrected for BSA.

Multiple-dose Toxicity

Multiple-dose toxicity studies with MMF were conducted in mice, rats, dogs, and monkeys as illustrated below; the duration of these studies ranged from 1 to 12 months by the oral route, and 2 weeks to 1 month by the intravenous route.

Table 12 Multiple-dose Toxicity Studies

Document No.	Study Type	Species	Dose (mg/kg/day)	Route	Duration[a]
Oral Toxicology Formulation:					
AT 5316	Subchronic	Mouse	0,6,25,100,300	Oral	3 months
AT 4155	Subchronic	Rat	0,3,9,30	Oral	1 month/1 month
AT 4831	Chronic	Rat	0,2,6,20	Oral	6 months/1 month
AT 6213	Chronic	Rat	0,2,6,15	Oral	12 months
AT 5105	Subchronic	Dog	0,6,20,60	Oral	3 months
AT 6214	Chronic	Dog	0,3,9,30	Oral	12 months/1 month
AT 4119	Subchronic	Monkey	0,15,45,150	Oral	1 month/1 month
AT 4858	Chronic	Monkey	0,6,20,70	Oral	6 months/1 month
Intravenous Toxicology Formulation:					
AT 5995	Subchronic	Rat	0,3,9,30	Intravenous	1 month

AT 6687	Subchronic	Monkey	0,50,100,200	Intravenous	2 weeks
AT 5997	Subchronic	Monkey	0,5,15,25	Intravenous	1 month

[a]Duration of dosing/duration of recovery period

Oral Dosing

The principal target organ systems in mice, rats, dogs, and monkeys dosed orally for up to 12 months with MMF were the hematopoietic and/or lymphoid systems. In these oral studies, the target organ changes were present at 100 mg/kg/day in the mouse, 6 mg/kg/day in the rat, 60 mg/kg/day in the dog, and 45 mg/kg/day in the monkey. Hematopoietic toxicity was evident in mice and rats primarily as decreased erythrocytic parameters and in dogs and monkeys primarily as decreased lymphocyte counts. Deaths related to anemia occurred in rats treated chronically with oral doses of 20 mg/kg/day. Lymphoid toxicity in rats, dogs, and monkeys included thymic atrophy and/or decreased numbers of active germinal centers in secondary lymphoid organs (lymph nodes, spleen, and/or intestine). Immunosuppression, the anticipated therapeutic mechanism, was achieved at or below no-effect dose levels for toxicity in subchronic/chronic studies in rat and monkey, as assessed *in vitro* by the effect of serum from dosed animals on lymphocyte mitogen response.

Recovery from the hematopoietic and lymphoid toxicity of MMF was observed in the rat 1- and 6-month studies after a one month postdosing recovery period. Evaluation of recovery was planned for the 1- and 6 month monkey studies, but could not be accomplished due to the premature demise or termination of animals in affected dose groups.

An increased incidence of viral (herpes virus B) and parasitic lesions occurred in monkeys after 3 months of dosing at 70 mg/kg/day. These effects involved a virus and an enzootic parasite known to be endemic in these feral animals, and were considered secondary to the expected pharmacologic (immunosuppressive) effects of MMF. No treatment-related infections occurred in the rodent or dog multiple-dose studies; the mice (CD-1®) and rats (CD®) used were virus-antibody free animals (VAF/Plus™, Charles River Laboratories).

Gastrointestinal and/or renal toxicity were present in the dog and the monkey at the higher dosages studied in these species. Multi-nucleated sperm precursors were present in the testes of monkeys at 1 month when treated with 150 mg/kg of MMF and at 3 or 6 months when treated with 70 or 20 mg/kg MMF, respectively. Dogs given oral doses of 60 mg/kg/day of MMF once daily for 3 months exhibited mortality and gastrointestinal erosion and necrosis. An increased frequency of diarrhea and soft feces occurred in dogs given 30 mg/kg/day for 1 year. Gastrointestinal and renal toxicity and associated mortality were present in monkeys given 150 mg/kg/day orally for 1 month.

Toxicokinetic data collected from the multiple-dose oral toxicity studies demonstrated dose-related increases in plasma concentrations of mycophenolic acid (MPA) and its glucuronide conjugate (MPAG), the principal metabolites of MMF. The approximate C_{max} and $AUC_{0\text{-}24\ hr}$ ranges for MPA corresponding with the doses of MMF (2 to 300 mg/kg/day) administered in the multiple-dose oral toxicity studies were 0.4 to 51.9 mcg/mL and 0.7 to 523 mcg•hr/mL, respectively. At a given oral dose of MMF, the resulting plasma levels of both MPA and MPAG tended to remain similar over a wide range of dosing duration (single dose up to 1 year dosing). There were no detectable levels of MMF in the plasma after oral administration of MMF.

Intravenous Dosing

Rats were given 1, 3, or 10 mg/mL MMF by intravenous infusion once daily for 28 days to deliver 3, 9, or 30 mg/kg/day. No treatment-related effects occurred at 3 or 9 mg/kg/day. At 30 mg/kg/day, decreased body weight gain, anemia, lymphoid atrophy, and decreased erythroid and increased myeloid cells in bone marrow were present. Injection site inflammatory changes suggestive of local irritation occurred at 30 mg/kg/day.

Monkeys were given 5 mg/mL MMF by intravenous infusion once daily for 0.5, 1, or 2 hours to deliver 50, 100, or 200 mg/kg/day, respectively, for 14 days. All monkeys survived the duration of treatment. Changes characteristic of local irritation were present in the veins of monkeys infused with MMF. At 200 mg/kg/day, decreased erythrocytic parameters in peripheral blood and reduced numbers of erythroid cells in the bone marrow were present. No other histopathologic signs of systemic toxicity occurred.

Monkeys were given 1, 3, or 5 mg/mL MMF by intravenous infusion once daily for 28 days to deliver 5, 15, or 25 mg/kg/day. Decreases in erythrocyte count, hemoglobin, and hematocrit were present at 25 mg/kg/day. Inflammatory changes suggestive of local irritation were present in injection veins of monkeys given 15 or 25 mg/kg/day. No histopathologic signs of systemic toxicity occurred.

Toxicokinetic data collected from the multiple-dose intravenous toxicity studies demonstrated dose-related increases in plasma concentrations of mycophenolic acid (MPA) and its glucuronide conjugate (MPAG), the principal metabolites of MMF. The approximate C_{max} ranges for MPA corresponding with the doses of MMF (3 to 200 mg/kg/day) administered in the multiple-dose intravenous toxicity studies were 5.9 to 215 mcg/mL. $AUC_{0\text{-}24\ hr}$ values were not determined as part of the intravenous toxicity studies. MMF was detected in plasma of monkeys dosed by intravenous infusion, when blood samples were collected during infusion.

Carcinogenicity:

Two-year bioassays with MMF were conducted in mice and rats as listed below in Table 13.

Table 13 Carcinogenicity Studies in Mice and Rats

Document No.	Study Type	Species	Dose (mg/kg/day)	Route	Duration
AT 6703	Carcinogenicity	Mouse	0,25,75,180	Oral	24 months (104 wks.)
AT 6702	Carcinogenicity	Rat	0,3,7,15	Oral	24 months (104 wks.)

Mice were dosed orally by gavage with MMF once daily for at least 104 weeks at 25, 75, and 180 mg/kg/day. MMF was not carcinogenic in the mouse. The highest dose, 180 mg/kg/day, was considered the maximum tolerated dose that could be administered based on treatment-related effects that included anemia, decreased numbers of erythrocytic cells and increased numbers of granulocytic cells and megakaryocytes in bone marrow, and increased granulopoiesis and lymphoid atrophy in spleen. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in BSA.

Rats were dosed orally by gavage with MMF once daily for at least 104 weeks at 3, 7, or 15 mg/kg/day. MMF was not carcinogenic in the rat. The highest dose, 15 mg/kg/day, was considered the maximum tolerated dose that could be administered based on treatment-related effects that included decreased survival (males), decreased body weight gain, and anemia. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see Table 16: Special Toxicity Studies).

Genotoxicity:

MMF was not genotoxic, with or without metabolic activation, in several assays: the bacterial mutation assay, the yeast mitotic gene conversion assay, the mouse micronucleus aberration assay, or the Chinese hamster ovary cell (CHO) chromosomal aberration assay.

A battery of *in vitro* and *in vivo* mutagenicity tests was performed with MMF. MPA was evaluated in a single-plate Ames assay.

Table 14: *In vitro* and *In vivo* Mutagenicity Studies

Document No.	Study Type	Species/Assay/Doses
MMF:		
AM 0312	Mutagenicity	*Salmonella typhimurium* (with and without activation). Ames mutation assay. 1-10,000 mcg per plate.
AM 0313	Mutagenicity	*Saccharomyces cerevisiae* (with and without activation). Mitotic gene conversion assay. 1-10,000 mcg/mL.
AM 0314	Mutagenicity	Chinese hamster ovary cells (with and without activation). Chromosomal aberration assay. 10-1,000 mcg/mL.
AM 0341	Mutagenicity	Chinese hamster ovary cells (with and without activation). Chromosomal aberration assay. 0.89-1293.1 mcg/mL.
AM 0315	Mutagenicity	Mouse micronucleus assay. 300, 1000, 3000 mg/kg. Oral. Single dose followed by 3 days of observation.
Mycophenolic Acid:		
AM 0207	Mutagenicity	*Salmonella typhimurium* (with and without activation). Ames (single plate) mutation assay (non-GLP screening study). 1-10,000 mcg per plate.

MMF did not induce point mutations (Ames assay) or primary DNA damage (yeast mitotic gene conversion assay) in the presence or absence of metabolic activation. In two assays for clastogenic effects, MMF was not mutagenic *in vivo* (mouse micronucleus assay) or *in vitro* with metabolic activation (Chinese hamster ovary [CHO] cell chromosomal aberration assay). Chromosome aberrations occurred in vitro without metabolic activation in the initial CHO cell chromosomal aberration assay but only at dose levels (249 to 300 mcg/mL) that were markedly cytotoxic, producing effects that included unhealthy cell monolayers, floating cellular debris, and few visible mitotic cells. No mutagenic activity was present with or without metabolic activation in a repeat CHO cell assay conducted at dose levels (0.89 to 5 mcg/mL) that were less overtly toxic. The highest dose for this repeat study produced targeted levels of toxicity in the cultured cells (50% to 80% reduction in mitotic index). Based on overall assessment of results from the two assays, the initial CHO cell assay without activation was considered to have produced false-positive results attributable to excessive cytotoxicity.

MPA did not induce point mutations in a single-plate Ames assay in the presence or absence of metabolic activation.

Reproductive and Developmental Toxicology:
Male and female reproduction studies, teratology studies, and a perinatal/postnatal reproduction study were conducted in rats and/or rabbits after oral dosing of MMF.

Table 15 Reproductive Toxicity Studies

Document No.	Study Type	Species	Dose (mg/kg)	Route
AT 4832	Male fertility & reproduction	Rat	0,2,6,20	Oral
AT 4987	Female fertility & reproduction	Rat	0,0.5,1.5,4.5	Oral
AT 4552	Teratology	Rat	0,0.6,2,6	Oral
AT 4667	Teratology	Rabbit	0,10,30,90	Oral
AT 6206	Perinatal/post-natal reproduction	Rat	0,1,3,10	Oral

Fertility and Reproduction (Segment I)

No treatment-related effects occurred in a male fertility and reproduction study conducted in rats dosed orally at 2, 6, or 20 mg/kg/day. The males were dosed as part of the 6-month toxicity study. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

In a female fertility and reproduction study conducted in rats dosed orally at 0.5, 1.5, or 4.5 mg/kg/day, the highest dose caused malformations (principally of the head and eyes) in the first-generation (F1) pups in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. The spectrum of malformations that occurred was similar to that present in the rat teratology study. No treatment-related effects on fertility were present in P1 females, P2 females, or P2 males. The no-observed-effect level was 1.5 mg/kg/day.

Teratology (Segment II)

Teratology studies were conducted by oral dosing in rats at 0.6, 2, or 6 mg/kg/day and in rabbits at 10, 30, or 90 mg/kg/day. Increased fetal resorptions and increased fetal malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day. These effects occurred in the absence of maternal toxicity. Principal malformations included head and ventral wall anomalies in the rat, and cardiovascular anomalies, ventral body wall fissures, renal anomalies, and oligopulmonism/hypopulmonism in the rabbit.

Decreased fetal weight also occurred in rats at 6 mg/kg/day. The no-effect levels for teratologic changes in rats and rabbits given MMF were 2 and 30 mg/kg/day, respectively.

Perinatal/Postnatal Reproduction (Segment III)

No adverse effects on parturition or the postnatal development of the offspring occurred when female rats were dosed orally at 1, 3, or 10 mg/kg/day.

Special Toxicology:

The special toxicity studies listed below were conducted with the oral formulation of MMF or with MPA.

Table 16 Special Toxicity Studies

Document No.	Study Type	Species	Dose (mg/kg/day)	Route	Duration[a]
MMF - Oral Toxicology Formulation:					
AT 6705	Neonatal Toxicity	Rat	0,3,9,30	Oral	1 month
AT 4671	Sensitization	Guinea Pig	4 mg per dose for 6 doses (10 mg/mL)	Dermal	1 month
AT 6143	Irritation	Rabbit	0.5 g	Dermal	4 hrs/3 days
AT 6123	Irritation	Rabbit	0.1 g	Ocular	Single/3 days
Mycophenolic Acid:					
AT 4664	Sensitization	Guinea Pig	4 mg per dose for 6 doses (10 mg/mL)	Dermal	1 month

[a]Duration of dosing/ Duration of observation period

Oral Toxicology Formulation

Neonatal (14 day-old) rats were given oral doses of 3, 9, or 30 mg/kg/day of MMF once daily for 4 weeks. Decreased body weight gain was present in males at 30 mg/kg/day and in females at 9 and 30 mg/kg/day. At 30 mg/kg/day, reduced red blood cell parameters, reduced bone marrow cellularity, reduced active lymphoid germinal centers, increased platelet counts, and increased splenic extramedullary hematopoiesis were present. No treatment-related effects occurred at 3 mg/kg/day.

Formulations of 10 mg/mL of MMF or MPA applied topically were not sensitizing in the guinea pig.

MMF was not an acute dermal irritant or an occular irritant when tested in rabbits.

Juvenile Toxicity: Not applicable

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrCellCept® i.v. (Lyophilized powder, 500 mg/vial), submission control 248429, Product Monograph, Hoffmann-La Roche Limited. JUN 10, 2021

.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Mycophenolate Mofetil for Injection USP
Powder for solution

Read this carefully before you start taking **Mycophenolate Mofetil for Injection USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Mycophenolate Mofetil for Injection USP**.

Serious Warnings and Precautions

- Mycophenolate Mofetil for Injection USP can cause **first trimester pregnancy loss (miscarriage) and birth defects** when used along with other medicines used to prevent organ rejection. You must not take Mycophenolate Mofetil for Injection USP if you are pregnant. Taking Mycophenolate Mofetil for Injection USP while pregnant can harm your unborn baby. Women must have two negative pregnancy tests before starting treatment with Mycophenolate Mofetil for Injection USP. Women must use two reliable forms of contraception at the same time while taking Mycophenolate Mofetil for Injection USP. See "Other warnings you should know about, Female Patients" for more information.
- Mycophenolate Mofetil for Injection USP **suppresses your immune system**. This can make you more likely to get **infections** and certain **cancers**, such as lymphoma.
- Mycophenolate Mofetil for Injection USP will be prescribed to you by a doctor with experience in medicines used to prevent organ rejection.

What is Mycophenolate Mofetil for Injection USP used for?

- Mycophenolate Mofetil for Injection USP is used after kidney, heart and liver transplantation to help prevent organ rejection.
- It is used along with other medicines including cyclosporine and medicines called corticosteroids. .

How does Mycophenolate Mofetil for Injection USP work?
Mycophenolate Mofetil for Injection USP works by slowing down your body's defense system (immune system). When you receive an organ transplant, Mycophenolate Mofetil for Injection USP prevents your body from rejecting this organ.

What are the ingredients in Mycophenolate Mofetil for Injection USP?
Medicinal ingredients: Mycophenolate mofetil (as mycophenolate mofetil hydrochloride).

Non-medicinal ingredients:

Citric acid, 5 mg, hydrochloric acid, 45.625 mg, polysorbate 80, 25 mg, and sodium hydroxide to adjust pH.

Mycophenolate Mofetil for Injection USP comes in the following dosage forms:
Mycophenolate Mofetil for Injection USP is available for patients who are unable to take oral medications. It comes as a powder for solution containing 500 mg mycophenolate mofetil.

Do not use Mycophenolate Mofetil for Injection USP if you:

- are allergic to mycophenolate mofetil or to mycophenolic acid.
- are allergic to any other ingredients in Mycophenolate Mofetil for Injection USP.

- are pregnant.
- are breastfeeding.
- are of childbearing age and are not using highly effective birth control.
- do not have results from a pregnancy test showing that you are not pregnant.
- are allergic to Polysorbate 80 (also known as TWEEN).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mycophenolate Mofetil for Injection USP. Talk about any health conditions or problems:

- If you are already on any immune suppressant treatment.
- Rare diseases called Lesch-Nyhan and Kelley-Seegmiller syndrome.
- Digestive problems, including ones with your stomach or bowels.
- Severe renal problems.

Other warnings you should know about:

Important warnings for women taking Mycophenolate Mofetil for Injection USP

- Do not take Mycophenolate Mofetil for Injection USP if you are pregnant.
- Mycophenolate Mofetil for Injection USP can cause first trimester pregnancy loss (miscarriage) and birth defects when used along with other medicines used to prevent organ rejection.
- These birth defects can affect the development of a baby's ears, limbs, face, heart, brain.
- You can only take Mycophenolate Mofetil for Injection USP if you are not pregnant and if you are using highly effective birth control.
- If you think you may be pregnant tell your doctor straight away. Keep taking Mycophenolate Mofetil for Injection USP until you see your doctor. They will talk to you about other medicines you can take to prevent rejection of your transplanted organ.
- Women who can get pregnant must have two negative blood or urine pregnancy tests. The second test should be performed 8-10 days after the first. You can only start Mycophenolate Mofetil for Injection USP if the tests are negative. You will be given repeat pregnancy tests during follow-up visits.
- You must always use two reliable methods of birth control:
    - Before you start taking Mycophenolate Mofetil for Injection USP,
    - During your entire treatment with Mycophenolate Mofetil for Injection USP and
    - For 6 weeks after stopping your treatment with Mycophenolate Mofetil for Injection USP .
- Talk to your doctor about the best methods of contraception for you. If you take oral contraceptives (birth control pills) while using Mycophenolate Mofetil for Injection USP you must also use another form of birth control method. This is because Mycophenolate Mofetil for Injection USP may make oral contraceptive less effective.
- **Do not** breastfeed your baby if you are taking Mycophenolate Mofetil for Injection USP as it may pass into breast milk and may harm your baby.
- Be sure to keep **all** appointments at your transplant clinic. During these visits, pregnancy tests may be administered by your doctor.

Important warnings for men taking Mycophenolate Mofetil for Injection USP:

- If you are a sexually active male, you must use effective birth control. Or, your female partner must use effective birth control while you are taking Mycophenolate Mofetil for Injection USP. Effective birth control must be used for at least 90 days after you stop taking Mycophenolate Mofetil for Injection USP.
- Men should not donate semen during therapy and for 90 days after taking of Mycophenolate Mofetil for Injection USP.

Serious infections and cancers:

- Mycophenolate Mofetil for Injection USP suppresses your immune system. This can make you more likely to get infections and certain cancers, such as lymphoma and skin cancer.
- Mycophenolate Mofetil for Injection USP slows down your immune system. This can affect your body's ability to fight infections. You are more likely to get infections when you take Mycophenolate Mofetil for Injection USP. Some

of these infections can be serious and fatal. Infections include: viral infections, a brain infection called progressive multifocal leukoencephalopathy, sepsis and other infections. It can also cause other infections to emerge in your body like hepatitis B or C or infections caused by polyomaviruses. See "Serious side effects and what to do about them" table for more information.

- Mycophenolate Mofetil for Injection USP increases your chances of getting certain cancers, especially skin cancer. See "Serious side effects and what to do about them" table for more information. You must limit the amount of sunlight and UV light you get. Do this by:
    - wearing protective clothing which also covers your head, neck, arms and legs.
    - using a sunscreen with a high sun protection factor (SPF).

Additional important warnings for all patients taking Mycophenolate Mofetil for Injection USP:

- Tell all health professionals you see that you are taking Mycophenolate Mofetil for Injection USP.
- Be sure to keep **all** appointments at your transplant clinic. During these visits, complete blood counts will need to be measured weekly in the first month, twice monthly for the second and third months of treatment, and then monthly for the remainder of the first year. Your doctor may sometimes order additional blood tests.
- You should not donate blood during therapy and for at least 6 weeks after taking Mycophenolate Mofetil for Injection USP.
- During treatment with Mycophenolate Mofetil for Injection USP, vaccinations may be less effective. Also, you should not receive live vaccines. Talk to your doctor before receiving any vaccines.
- Mycophenolate Mofetil for Injection USP may affect your ability to drive and use machines. Before driving or using machines, wait until you are feeling well again.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Mycophenolate Mofetil for Injection USP:

- Acyclovir, an antiviral medication;
- Ganciclovir or valganciclovir, antiviral medications;
- Isavuconazole, an antiviral medication;
- Tacrolimus, used to suppress the body's immune system;
- Telmisartan, used to treat high blood pressure;
- Rifampicin, an antibiotic;
- Azathioprine, used to suppress the body's immune system;
- Antacids, which neutralize stomach acidity;
- Proton pump inhibitors, such as lansoprazole and pantoprazole;
- Renagel® (sevelamer), or other calcium free phosphate binders;
- Cholestyramine, which is used to treat high blood cholesterol.
- Combinations of antibiotics taken at the same time.

How to take Mycophenolate Mofetil for Injection USP:

- Mycophenolate Mofetil for Injection USP will be given to you by a healthcare professional.
- It will be infused directly into your vein.
- Mycophenolate Mofetil for Injection USP will be given to you as soon as possible after transplantation
- Mycophenolate Mofetil for Injection USP must be taken with other immunosuppressive medicines (such as cyclosporine and corticosteroids). Discuss with your doctor if you are to stop, or to continue, the other immunosuppressant drugs you had been taking.

Usual Dose:

Your doctor will decide what dose of Mycophenolate Mofetil for Injection USP you will get and when you will get it.

Kidney Transplant Adults:

- A dose of 1 g administered intravenously (over 2 hours) twice a day (daily dose of 2 g) is recommended after kidney transplantation.

Heart Transplant Adults:

- A dose of 1.5 g administered intravenously (over **no less than 2 hours**) twice a day (daily dose of 3 g) is recommended after heart transplantation in adults.

Liver Transplant Adults:

- A dose of 1 g administered intravenously (over **no less than 2 hours**) twice a day (daily dose of 2 g) is recommended after liver transplantation in adults.

Overdose:

If you think you, or a person you are caring for, have taken too much Mycophenolate Mofetil for Injection USP, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of Mycophenolate Mofetil for Injection USP, your doctor will decide when you should receive your next dose.

What are possible side effects from using Mycophenolate Mofetil for Injection USP?

These are not all the possible side effects you may have when taking Mycophenolate Mofetil for Injection USP. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom/effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Abdominal pain		✓	
Blood in urine		✓	
Constipation		✓	
Increased cough		✓	
Diarrhea		✓	
Fever		✓	
Laboured breathing		✓	
Headache		✓	
High blood pressure		✓	
Swelling of parts of your body		✓	
Vomiting		✓	
Weakness		✓	
COMMON			
Chest or back pain		✓	
Dizziness		✓	

Heart burn		✓	
Involuntary trembling		✓	
Muscle weakness		✓	
Nausea		✓	
Nosebleed		✓	
Sleeplessness		✓	
Stomach Pain		✓	
Sepsis (severe infection): fever and chills, low body temperature, fast heartbeat, nausea and vomiting		✓	
Gastrointestinal perforation (a hole in your stomach or bowels): chills or fever, nausea, severe abdominal pain, vomiting		✓	
RARE			
Blood or black tarry stools		✓	
UNKNOWN			
Progressive multifocal leukoencephalopathy (infection of the brain): loss of coordination, difficulty walking, facial drooping, loss of vision, trouble speaking		✓	
Infections: body aches and pains, boils on your skin, chills, cold symptoms, earache, flu-like symptoms, headache, pain when you urinate, sore throat, cuts and scrapes that are red, have pus or don't heal.		✓	
Pure red cell aplasia (bone marrow stops producing red cells): dizziness, fainting, fatigue, feeling unwell, pale skin, pale stools, rapid heartbeat, shortness of breath, weakness		✓	
Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms.		✓	
Bone marrow suppression (a large decrease in the production of blood cells and platelets by the bone marrow): fatigue, increased heart rate, unexpected bruising, bleeding; paleness of the skin, lips, and bail beds; dizziness		✓	
BK virus-associated nephropathy (kidney disease due to an infection): changes in vision, like blurred vision; changes in the color of your urine (urine that is brown or red in color); difficulty urinating; needing to urinate more than is normal for you; a cough, cold, or trouble breathing; fever, muscle pain, or weakness		✓	
Certain types of cancers (such as lymphoma and skin cancer): new moles, skin lesions or bumps; change in the size or colour of a mole, moles with uneven borders or that are asymmetric, fever, prolonged tiredness, weight loss, lymph node swelling, a change in your bowel or bladder habits, unusual bleeding or discharge, the		✓	

appearance of a lump or thickened areas in your breast or anywhere else on your body, unexplained stomach upset or any trouble with swallowing, a nagging cough or hoarseness, night sweats			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep Mycophenolate Mofetil for Injection USP out of reach and sight of children**. A child who accidentally takes the drug may be seriously harmed. A locked drawer or cupboard is best if you have small children in the house.
- Mycophenolate Mofetil for Injection USP, powder for solution should be stored at room temperature (15ºC- 30ºC). The healthcare professional will store the reconstituted/infusion solutions at room temperature (15ºC- 30ºC).
- Mycophenolate Mofetil for Injection USP should not be used after the expiry date (EXP) shown on the package.

If you want more information about Mycophenolate Mofetil for Injection USP:

- Talk to your healthcare professional
- Find the full product monograph, that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, http://www.sterimaxinc.com, or by contacting the sponsor, SteriMax Inc., at: 1-800-881-3550

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