PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-MYCOPHENOLIC ACID

Mycophenolic acid delayed-release tablets

Delayed-release tablets, 180 mg and 360 mg mycophenolic acid (as mycophenolate sodium), Oral

USP

Immunosuppressant
ATC code: L04AA06

APOTEX INC.
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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

None at the time of authorisation

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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

APO-MYCOPHENOLIC ACID (mycophenolate sodium) is indicated for:

- the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, and corticosteroids.

1.1 Pediatrics

Safety and efficacy in pediatric patients have not been established. Limited pharmacokinetic data are available for pediatric renal transplant patients (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics).

1.2 Geriatrics

Patients > 65 years may generally be at increased risk of adverse drug reactions due to an immunosuppression. Based on the controlled mycophenolate sodium clinical trials, patients > 65 receiving mycophenolate sodium as part of a combination immunosuppressive regimen, did not show an increased risk of adverse reactions, compared to younger patients.

No dose adjustment is required in this patient population.

2 CONTRAINDICATIONS

- APO-MYCOPHENOLIC ACID (mycophenolate sodium) is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients (see 6 DOSAGE FORMS, STRENGTH, COMPOSITION AND PACKAGING).
- APO-MYCOPHENOLIC ACID is contraindicated during pregnancy due to its mutagenic and teratogenic potential.
- APO-MYCOPHENOLIC ACID is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see 7.1.1 Pregnant Women).
- APO-MYCOPHENOLIC ACID should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.
- APO-MYCOPHENOLIC ACID is contraindicated in women who are breastfeeding.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from immunosuppression. Only physicians experienced in

immunosuppressive therapy and management of solid organ transplant patients should prescribe APO-MYCOPHENOLIC ACID (mycophenolate sodium). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

- Female users of childbearing potential must use contraception. Use of APO-MYCOPHENOLIC ACID during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- APO-MYCOPHENOLIC ACID should be used in combination with cyclosporine and corticosteroid therapy.
- APO-MYCOPHENOLIC ACID should be taken on an empty stomach, one hour before or two hours after food intake (see 9.5 Drug-Food Interactions).

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose in adults is 720 mg (four 180 mg or two 360 mg tablets) administered twice daily (1.440 g total daily dose).
- *Geriatric Use*: No dose adjustments are required. The recommended dose is 720 mg administered twice daily.
- *Pediatric Use*: Safety and efficacy in pediatric patients have not been established. Limited pharmacokinetic data are available for pediatric renal transplant patients. (see 10.3 Pharmacokinetics Special Populations and Conditions, Pediatrics)
- *Treatment during Rejection Episodes*: Renal transplant rejection does not affect MPA pharmacokinetics; dosage reduction or interruption of APO-MYCOPHENOLIC ACID is not required.
- *Patients with Renal Impairment*: No dose adjustments are needed in patients experiencing delayed post-operative renal graft function. Patients with severe chronic renal impairment (GFR < 25 mL/min[1]/1.73 m[2]) should be carefully monitored.
- *Patients with Hepatic Impairment*: No dose adjustments are needed for renal transplant patients with hepatic parenchymal disease.

- *Patients Developing Neutropenia*: If neutropenia develops (ANC < 1.3×10^3 /mcL), dosing with APO-MYCOPHENOLIC ACID should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

4.3 Reconstitution

Not Applicable

4.4 Administration

- Patients are to be instructed that APO-MYCOPHENOLIC ACID tablets should not be crushed, chewed, or cut prior to ingesting but to be swallowed whole in order to maintain the integrity of the enteric coating.

4.5 Missed Dose

Not applicable

5 OVERDOSAGE

There have been anecdotal reports of deliberate or accidental overdoses with mycophenolate sodium, whereas not all patients experienced related adverse events.

In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class. Accordingly an overdose of mycophenolate sodium could possibly result in over suppression of the immune system and may increase the susceptibility to infection including opportunistic infections, fatal infections and sepsis. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count < 1.5 x 10^3 / micro L or anaemia) it may be appropriate to interrupt or discontinue APO-MYCOPHENOLIC ACID (see 7 WARNINGS AND PRECAUTIONS, Hematology and 8.2 Clinical Trail Adverse Reactions).

Possible signs and symptoms of acute overdose could include the following: hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and vomiting, and dyspepsia. General supportive measures and symptomatic treatment should be followed in all cases of over dosage. Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA due to the 98% plasma protein binding of MPA. By interfering with enterohepatic circulation of MPA, activated charcoal or bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

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	Non-medicinal Ingredients
oral	Enteric Coated Tablets equivalent to 180 mg and 360 mg mycophenolic acid (as mycophenolate sodium)	colloidal silicon dioxide, methylcellulose, sodium lauryl sulfate, and stearic acid. The enteric coating of the tablet consists of hydroxypropyl methylcellulose, methacrylic acid copolymer, polyethylene glycol, talc, titanium dioxide, triethyl citrate, yellow iron oxide, FD&C Blue No. 2 (180 mg) and red iron oxide (360 mg).

APO-MYCOPHENOLIC ACID 180 mg tablets contain 180 mg of mycophenolic acid as mycophenolate sodium: Light green, round, slightly biconvex beveled edge enteric coated tablet. Engraved with "MYC" over "180" on one side, "APO" on the other side. Available in bottles of 100 enteric coated tablets, and unit dose of 10 tablets per blister pack; 12 blister packs/carton.

APO-MYCOPHENOLIC ACID 360 mg tablets contain 360 mg of mycophenolic acid as mycophenolate sodium: Light pink, oval, biconvex enteric coated tablet. Engraved with "APO" on one side, "MYC 360" on the other side. Available in bottles of 100 enteric coated tablets, and unit dose of 10 tablets per blister pack; 12 blister packs/carton.

7 WARNINGS AND PRECAUTIONS

General

Patients receiving APO-MYCOPHENOLIC ACID should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.

Carcinogenesis and Mutagenesis

Patients receiving immunosuppressive regimens involving combinations of drugs, including APO-MYCOPHENOLIC ACID, as part of an immunosuppressive regimen are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be

related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimize the 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.

Endocrine and Metabolism

On theoretical grounds, because APO-MYCOPHENOLIC ACID is an IMPDH Inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Gastrointestinal

Because mycophenolic acid derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, APO-MYCOPHENOLIC ACID should be administered with caution in patients with active serious digestive system disease. Gastrointestinal adverse events are common in patients receiving MPA treatment. Gastrointestinal bleeding (requiring hospitalization), gastrointestinal tract ulceration, and perforation have rarely been reported in *de novo* renal transplant patients or maintenance patients treated with mycophenolic acid enteric coated tablets during clinical trials. Most patients receiving mycophenolic acid enteric coated tablets were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate sodium.

Hematologic

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate sodium or mycophenolate mofetil (MMF) in combination with other immunosuppressive agents (see 8.5 Post-Market Adverse Reactions). The mechanism for mycophenolate sodium or MMF-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with mycophenolate sodium. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to APO-MYCOPHENOLIC ACID therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Patients receiving APO-MYCOPHENOLIC ACID should be monitored for blood dyscrasias (e.g. neutropenia or anemia) (see 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests). The development of neutropenia may be related to mycophenolate sodium itself, concomitant medications, viral infections, or some combination of these events. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count [ANC < 1.5×10^3 /mcL] or anemia), dosing with APO-MYCOPHENOLIC ACID should be interrupted or the dose reduced,

appropriate diagnostic tests performed, and the patient managed appropriately (see 4.2 Recommended Dose and Dosage Adjustment).

Hepatic/Biliary/Pancreatic

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of APO-MYCOPHENOLIC ACID with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of APO-MYCOPHENOLIC ACID.

Immune

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate sodium and mycophenolate mofetil (MMF) which both metabolize to the same active form of mycophenolic acid (MPA) in the body. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including treatment with immunosuppressants and impairment of immune functions. 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. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection (BK virus associated nephropathy [BKVAN]), should be included in the differential diagnosis in immunosuppressed patients with deteriorating renal function (see 8.5 Post-Market Adverse Reactions). Consideration should be given to reducing the amount of immunosuppression in patients who develop PML or PVAN. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

PVAN and BKVAN are associated with serious outcomes, sometimes leading to renal graft loss (see 8.5 Post-Market Adverse Reactions). Patient monitoring may help detect patients at risk for polyomavirus or BK virus-associated nephropathy.

Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives mycophenolate sodium and MMF. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Monitoring and Laboratory Tests

Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If neutropenia develops (ANC < 1.3×10^3 /mcL) dosing with APO-MYCOPHENOLIC ACID should be

interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Renal

Subjects with severe chronic renal impairment (GFR < 25 mL/min/1.73 m^2) may present higher plasma MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

In the *de novo* study, 18.3% of mycophenolate sodium patients versus 16.7% in the MMF group experienced delayed graft function (DGF). Patients with DGF experienced a higher incidence of certain adverse events such as anemia, leukopenia, and hyperkalemia than patients without DGF, but these events in DGF patients were not more frequent in patients receiving mycophenolate sodium than MMF. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (see 4.2 Recommended Dose and Dose Adjustment).

Reproductive Health: Female and Male Potential

- **Fertility**

  Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day. The systemic exposure at this dose represents approximately 9 times the clinical exposure at the tested clinical dose of 1.44 g/day mycophenolate sodium. No effects on female fertility were seen up to a dose of 20 mg/kg/day, a dose at which maternal toxicity and embryotoxicity were already observed and yielding an exposure similar to that observed at the maximum recommended clinical dose.

- **Contraception**

  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, including at least one highly effective method, before beginning APO-MYCOPHENOLIC ACID therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

  Prior to starting therapy with APO-MYCOPHENOLIC ACID, 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, if feasible, should be performed 8 to 10 days after the first one and immediately before starting APO-MYCOPHENOLIC ACID. 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.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients are recommended to use highly effective contraception during treatment and for total of 90 days after the last dose of APO-MYCOPHENOLIC ACID (see 9.4 Drug-Drug Interactions). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

Sensitivity/Resistance

***Vaccinations*:** During treatment with APO-MYCOPHENOLIC ACID, patients should be advised that during treatment with MPA, vaccinations may be less effective and the use of live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to National Guidelines for influenza vaccination.

7.1 Special Populations

7.1.1 Pregnant Women

APO-MYCOPHENOLIC ACID is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. APO-MYCOPHENOLIC ACID should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see 2 CONTRAINDICATIONS and 8.5 Post Market Adverse Reactions). Mycophenolate sodium is a powerful teratogen and mutagen. Spontaneous abortion (rate of 45 to 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 to27%) have been reported following mycophenolate mofetil (MMF) exposure during pregnancy. For comparison the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4 to 5 % in solid organ transplant patients treated with immunosupressants other than mycophenolate mofetil (see 8.5 Post Market Adverse Reactions).

Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY: Reproductive and Developmental Toxicity).

7.1.2 Breast-feeding

APO-MYCOPHENOLIC ACID is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see 2 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

See 1.1 Pediatrics.

7.1.4 Geriatrics

See 1.2 Geriatrics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common (>25%) adverse events from clinical trial data from *de novo* kidney transplant patients treated with mycophenolate sodium include constipation, nausea, and urinary tract infection. Clinical trial data from maintenance patients treated with mycophenolate sodium show that nausea, diarrhea and nasopharyngitis were the most frequently observed adverse reactions (> 15%). Fatal infections were rarely observed in patients receiving mycophenolate sodium (0.5%) in controlled clinical trials.

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

The incidence of adverse events for mycophenolate sodium was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in *de novo* and maintenance kidney transplant patients.

Adverse events reported in > 10% of patients receiving mycophenolate sodium or MMF in the 12-months *de novo* renal study and maintenance renal study, when used in combination with cyclosporine are listed in Table 2. Adverse event rates were similar between mycophenolate sodium and MMF in both *de novo* and maintenance patients.

Table 2: Adverse Events (%) in Controlled *de novo* and Maintenance Renal Studies Reported in ≥ 10% of Patients

	***de novo* Renal Study**		**Maintenance Renal Study**	
	Mycophenolate sodium 1.44 g/day (n=213)	**MMF 2 g/day (n=210)**	**Mycophenolate sodium 1.44 g/day (n=159)**	**MMF 2 g/day (n=163)**
Blood and lymphatic system disorders				
Anemia	21.6	21.9	-	-
Leukopenia	19.2	20.5	-	-
Gastrointestinal system disorders				
Constipation	38	39.5	-	-
Nausea	29.1	27.1	24.5	19
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23	20	15.1	12.9
Dyspepsia	22.5	19	13.8	14.7
Upper abdominal pain	14.1	14.3	-	-
General and administrative site disorders				
Edema	16.9	17.6	-	-
Edema lower limb	15.5	17.1	-	-
Edema peripheral	-	-	10.7	12.3
Pyrexia	12.7	18.6	-	-
Pain	13.6	8.6	-	-
Infections and infestations				
Urinary tract infection	29.1	33.3	10.1	11.7
CMV infection	20.2	18.1		
Nasopharyngitis	-	-	16.4	19.6
Upper respiratory tract infection	-	-	12.6	9.8
Investigations				
Increased blood creatinine	14.6	10	-	-
Metabolism and nutrition disorder				
Hypocalcemia	11.3	15.2	-	-
Hyperuricemia	12.7	13.3	-	-
Hyperlipidemia	12.2	9.5	-	-
Hypokalemia	12.7	9	-	-
Hypophosphatemia	10.8	8.6	-	-
Musculoskeletal, connective tissue and bone disorder				
Back pain	11.7	6.2	-	-
Arthralgia	-	-	13.8	9.8

	de novo Renal Study		Maintenance Renal Study	
	Mycophenolate sodium 1.44 g/day (n=213)	**MMF 2 g/day (n=210)**	**Mycophenolate sodium 1.44 g/day (n=159)**	**MMF 2 g/day (n=163)**
Nervous system disorder				
Insomnia	23.5	23.8	-	-
Tremor	11.7	14.3	-	-
Headache	13.1	11	17.6	16.6
Respiratory, thoracic and mediastinal disorder				
Cough	-	-	11.3	8
Surgical and medical procedure				
Post-operative pain	23.9	18.6	-	-
Vascular disorder				
Hypertension	18.3	18.1	-	-

Table 3 summarizes the incidence of opportunistic infections in *de novo* and maintenance transplant patients, which were similar in both treatment groups.

Table 3: Viral and Fungal Infections (%) Reported Over 0 to12 Months

	de novo Renal Study		Maintenance Renal Study	
	Mycophenolate sodium 1.44 g/day (n = 213)	**MMF 2 g/day (n = 210)**	**Mycophenolate sodium 1.44 g/day (n = 159)**	**MMF 2 g/day (n = 163)**
	(%)	(%)	(%)	(%)
Any cytomegalovirus - Cytomegalovirus disease	21.6 4.7	20.5 4.3	1.9 0	1.8 0.6
Herpes simplex	8	6.2	1.3	2.5
Herpes zoster	4.7	3.8	1.9	3.1
Any fungal infection - Candida NOS - Candida albicans	10.8 5.6 2.3	11.9 6.2 3.8	2.5 0 0.6	1.8 1.8 0

Long term administration of mycophenolate sodium (up to 30 months of exposure) did not show any unexpected changes in the pattern of adverse events including infections and malignancies.

The following adverse events were reported between 3% to <10% incidence in *de novo* and maintenance patients treated with mycophenolate sodium in combination with cyclosporine and corticosteroids are listed in Table 4.

Table 4: Adverse Events Reported in 3% to <10% of Patients Treated with Mycophenolate Sodium in Combination with Cyclosporine and Corticosteroids

	de novo **Renal Study**	**Maintenance Renal Study**
Blood and lymphatic disorders	Lymphocele, thrombocytopenia	Leukopenia, anemia
Cardiac disorder	Tachycardia	-
Eye disorder	Vision blurred	-
Endocrine disorders	Cushingoid, hirsutism	-
Gastrointestinal disorder	Flatulence, abdominal distension, sore throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool	Abdominal pain, constipation, gastroesophageal reflux disease, loose stool, flatulence, abdominal pain upper
General disorders and administration site conditions	Fatigue, edema peripheral, chest pain	Fatigue, pyrexia, edema, chest pain
Infections and infestations	Nasopharyngitis, herpes simplex, upper respiratory tract infection, oral candidiasis, herpes zoster, sinusitis, wound infection, implant infection, pneumonia	Influenza, sinusitis
Injury, poisoning, and procedural complications	Drug toxicity	Post procedural pain
Investigations	Hemoglobin decrease, blood pressure increased, liver function tests abnormal	Blood creatinine increase, weight increase
Metabolism and nutrition disorders	Hypercholesterolemia, hyperkalemia, hypomagnesemia, diabetes mellitus, hyperphosphatemia, dehydration, fluid overload, hyperglycemia, hypercalcemia	Dehydration, hypokalemia, hypercholesterolemia
Musculoskeletal and connective tissue disorders	Arthralgia, pain in limb, muscle cramps, myalgia	Pain in limb, back pain, muscle cramps, peripheral swelling, myalgia
Nervous system disorders	Dizziness (excluding vertigo)	Dizziness

	de novo Renal Study	Maintenance Renal Study
Psychiatric disorders	Anxiety	Insomnia, depression
Renal and urinary disorders	Renal tubular necrosis, renal impairment, dysuria, hematuria, hydronephrosis, bladder spasm, urinary retention	-
Respiratory, thoracic and mediastinal disorders	Cough, dyspnea, dyspnea exertional	Dyspnea, pharyngolaryngeal pain, sinus congestion
Skin and subcutaneous tissue disorder	Acne, pruritus	Rash, contusion
Surgical and medical procedures	Complications of transplant surgery, post operative complications, post operative wound complication	-
Vascular disorder	Hypertension aggravated, hypotension	Hypertension

The following opportunistic infections occurred rarely in the above controlled trials: aspergillus and cryptococcus.

The incidence of malignancies and lymphoma is consistent with that reported in the literature for this patient population. Lymphoma developed in 2 *de novo* patients (0.9%), (one diagnosed 9 days after treatment initiation) and in 2 maintenance patients (1.3%) (one was AIDS-related), receiving mycophenolate sodium with other immunosuppressive agents in the 12-month controlled clinical trials. Non-melanoma skin carcinoma occurred in 0.9% *de novo* and 1.8% maintenance patients. Other types of malignancy occurred in 0.5% *de novo* and 0.6% maintenance patients.

Adverse Events Associated with MPA

The following adverse reactions have been associated with MPA (including MMF):

Gastrointestinal: colitis (sometimes caused by CMV), pancreatitis, esophagitis, intestinal perforation, gastrointestinal hemorrhage, gastric ulcers, duodenal ulcers, and ileus.

Respiratory: although not reported with mycophenolate sodium, interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely with MPA administered as MMF and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post transplant patients receiving MPA derivatives.

Infections and Infestation: Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate sodium and mycophenolate mofetil (MMF) (see 7 WARNINGS AND PRECAUTIONS, Immune).

Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection is attributed to mycophenolic acid compounds (including mycophenolate sodium) as a class effect (see 7 WARNINGS AND PRECAUTIONS, Immune).

Blood and Lymphatic system disorders: Agranulocytosis, neutropenia, pancytopenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid compounds (including mycophenolate sodium) in combination with other immunosuppressive agents (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

8.5 Post-Market Adverse Reactions

The post marketing data of pregnant women exposed to mycophenolate mofetil (MMF) indicate that use of MPA during pregnancy is associated with an increased risk of congenital disorders and first trimester pregnancy loss.

Congenital Disorders:

Congenital malformations, including multiple malformations, have been reported postmarketing, in children of patients exposed to MPA in combination with other immunosuppressants during pregnancy.

The following malformations were most frequently reported:

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

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

Pregnancy, Puerperium and Perinatal Conditions:

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

Skin and subcutaneous tissue disorders:

Rash has been identified as an adverse drug reaction from post-approval clinical trials, post-marketing surveillance and spontaneous reports.

General disorders and administration site conditions: de novo purine synthesis inhibitors-associated acute inflammatory syndrome

Immune System Disorders:

Hypogammaglobulinemia:

There have been reports of hypogammaglobulinemia in adult patients treated with mycophenolate mofetil or mycophenolic acid in combination with other immunosuppressants. Consideration should be given, in patients developing recurrent infections, to have their serum immunoglobulins measured and monitored as needed.

Musculoskeletal and connective tissue disorders: asthenia

Respiratory Disorders:

Bronchiectasis:

In transplant patients treated with mycophenolate sodium in combination with other immunosuppressants, cases of bronchiectasis have been reported. Considerations should be given, in patients developing persistent pulmonary symptoms such as cough, dyspnea or recurring respiratory infections, to investigate further to determine definitely if they present bronchiectasis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Mycophenolate sodium has been administered in combination with the following agents in clinical trials: antilymphocyte/thymocyte immunoglobulin, Simulect® (basiliximab), daclizumab, muromonab, cyclosporine, Prograf* (tacrolimus) and corticosteroids. The efficacy and safety of

the use of mycophenolate sodium with other immunosuppressive agents have not been studied.

9.4 Drug-Drug Interactions

Table 5: Established or Potential Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
Antacids /Antacids with magnesium and aluminium hydroxides	Single-dose of mycophenolate sodium administered to 12 stable renal transplant patients alone and in combination with Maalox* (30 mL).	Absorption of a single dose of mycophenolate sodium was decreased when administered in combination with Maalox* (30 mL). The C_{max} and $AUC_{(0-T)}$ for MPA were 25% and 37% lower, respectively, than when mycophenolate sodium was given alone.	Magnesium-aluminum containing antacids may be used intermittently (several doses/week) for the treatment of occasional dyspepsia. However, the chronic daily use of magnesium-aluminum containing antacids with APO-MYCOPHENOLIC ACID is not recommended due to the potential for decreased MPA exposure.
Antibiotics eliminating β-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin	Cellcept*	These types of antibiotics are postulated to interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure.	Clinical relevance is unclear

Drug	Reference	Effect	Clinical Comment
classes of antibiotics)			
Cyclosporine	Stable renal transplant patients.	Cyclosporine pharmacokinetics were unaffected by steady-state dosing of mycophenolate sodium.	--
Acyclovir	CellCept* Prescribing Information.	Higher plasma concentrations of both MPAG (mycophenolic acid glucuronide) and Acyclovir may occur in the presence of renal impairment.	The potential exists for these two drugs to compete for tubular secretion, resulting in a further increase in the concentration of both MPAG and Acyclovir. In this situation patients should be carefully followed up.
Gancyclovir	CellCept* Prescribing Information.	MPA and MPAG pharmacokinetics are unaffected by the addition of Gancyclovir. The clearance of Gancyclovir is unchanged in the setting of therapeutic MPA exposure.	In patients with renal impairment in which APO-MYCOPHENOLIC ACID and Gancyclovir are coadministered the dose recommendations for Gancyclovir should be observed and patients monitored carefully.

Drug	Reference	Effect	Clinical Comment
Tacrolimus/ Neoral®	Calcineurin cross-over study in stable renal transplant patients	Mean MPA AUC was 19% higher and C_{max} approximately 20% lower. Mean MPAG AUC and C_{max} were approximately 30% lower on tacrolimus treatment compared to Neoral® treatment	--
Azathioprine/ mycophenolate mofetil	CellCept* Prescribing Information.	Inhibition of purine metabolism.	Given that azathioprine and mycophenolate mofetil inhibit purine metabolism, it is recommended that APO-MYCOPHENOLIC ACID not be administered concomitantly with azathioprine or mycophenolate mofetil.
Cholestyramine and drugs that bind bile acids	CellCept* Prescribing Information.	Concomitant administration of cholestyramine leads to a reduction in the AUC of MPA.	Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of APO-MYCOPHENOLIC ACID.

Drug	Reference	Effect	Clinical Comment
Oral contraceptives	CellCept* Prescribing Information.	None	Although not measured in a clinical trial, given the different metabolism of mycophenolate sodium and oral contraceptives, no drug interaction between these two classes of drug is expected, however, given that the long term effect of mycophenolate sodium dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected.
Proton Pump inhibitors	Clinical Expert Report	In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of mycophenolate sodium and pantoprazole.	

*All trademarks and registered trademarks are the property of their respective owners. SIMULECT and NEORAL are registered trademarks.

9.5 Drug-Food Interactions

Compared to the fasting state, administration of mycophenolate sodium 720 mg with a high fat meal (55g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA. However, there was a 33% decrease in the maximal concentration (C_{max}) of MPA, significant delays in

absorption of MPA (T_{max} delayed up to 20 hours) were observed. To avoid variations in MPA absorption between doses, APO-MYCOPHENOLIC ACID should be taken on an empty stomach (see 4.1 Dosing Considerations).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APO-MYCOPHENOLIC ACID (mycophenolate sodium), deliver the active moiety, mycophenolic acid (MPA). 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 to 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 a potent cytostatic effect on lymphocytes. Thus the mode of action is complementary to calcineurin inhibitors which interfere with cytokine transcription and resting T-lymphocytes.

Mycophenolate sodium has been shown to prevent the occurrence of acute rejection in models of kidney allotransplantation, of heart allotransplantation and of heart xenotransplantation associated or not with other immunosuppressive treatment. Mycophenolate sodium also inhibited proliferative arteriopathy in experimental models of aortic allografts in rats as well as antibody production in mice.

10.2 Pharmacodynamics

Not available at the time of authorization

10.3 Pharmacokinetics

Table 6: Mean (±SD) Pharmacokinetic Parameters for MPA following Oral Administration of Mycophenolate Sodium to Renal Transplant Patients on Cyclosporine Based Immunosuppression

Study Patient	Mycophenolate Sodium Dosing	N	Dose (mg)	T_{max}* (hr)	C_{max} (mcg/ml)	AUC_{0-12hr} (mcg*hr/ml)
Adult	Single	24	720	2(0.8 to8)	26.1±12.0	66.5 ±22.6**

Study Patient	Mycophenolate Sodium Dosing	N	Dose (mg)	T_{max}* (hr)	C_{max} (mcg/ml)	AUC_{0-12hr} (mcg*hr/ml)
Pediatric***	Single	10	450/m^2	2.5(1.5 to 24)	36.3± 20.9	74.3± 22.5**
Adult	Multiple x 6 days, BID	10	720	2(1.5 to3.0)	37.0 ±13.3	67.9± 20.3
Adult	Multiple x 28 days, BID	36	720	2.5(1.5 to 8)	31.2± 18.1	71.2 ±26.3
Adult	Chronic, Multiple dose, BID					
	2 weeks post-transplant	12	720	1.8(1.0 to5.3)	15.0 ±10.7	28.6 ±11.5
	3 months post-transplant	12	720	2(0.5 to 2.5)	26.2 ±12.7	52.3 ±17.4
	6 months post-transplant	12	720	2(0 to 3)	24.1± 9.6	57.2± 15.3
Adult	Chronic, Multiple dose, BID	18	720	1.5(0 to 6)	18.9 ±7.9	57.4± 15.0

* median (range), ** AUC_{0-8}, *** age range of 5 - 16 years

The mean pharmacokinetic parameters for MPA following the administration of mycophenolate sodium in renal transplant patients on cyclosporine based immunosuppression are shown in Table 6. Single dose mycophenolate sodium pharmacokinetics predict multiple dose pharmacokinetics. However, in the early post transplant period, mean MPA AUC and C_{max} were approximately one-half of those measured six months post transplant.

After near equimolar dosing of mycophenolate sodium (720 mg BID) and MMF (1000 mg BID) in both the single and multiple dose cross-over trials, mean systemic MPA exposure was similar.

Absorption:

In vitro studies demonstrated that the mycophenolate sodium does not release MPA under acidic conditions (pH < 5) as in the stomach but is highly soluble in neutral pH conditions as in the intestine. Following mycophenolate sodium oral administration without food, consistent with its enteric-coated formulation, the median time to maximum concentration (T_{max}) of MPA was 1.5 - 2.5 hours (range: 1.5 to 8 hours) compared to 1 hour (range: 0.5 to 3 hours) for mycophenolate mofetil (MMF). In stable renal transplant patients on cyclosporine based immunosuppression, gastrointestinal absorption of MPA was 93% and absolute bioavailability 71%. Mycophenolate sodium pharmacokinetics is dose proportional over the dose range of 180 to 2160 mg.

Food effect: Compared to the fasting state, administration of mycophenolate sodium 720 mg with a high fat meal (55 g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA. However, there was a 33% decrease in the maximal concentration (C_{max}) of MPA, significant delays in absorption of MPA (T_{max} delayed up to 20 hours) were observed. To avoid variations in MPA absorption between doses, APO-MYCOPHENOLIC ACID should be taken on an empty stomach (see 4.1 Dosing Considerations).

Distribution:

The volume of distribution at steady-state for MPA is 54.3 (± 25.2) L. MPA is highly protein bound to albumin, >98%. The protein binding of mycophenolic acid glucuronide (MPAG) is 82%. The free MPA concentration may increase under conditions of decreased protein binding (uremia, hepatic failure, and hypoalbuminemia). This may put patients at an increased risk of MPA-related adverse events.

Metabolism:

The half-life of MPA is 11.7 (± 3.2) hours and the clearance is 8.4 (± 1.8) L/hr. MPA is metabolized principally by glucuronyl transferase to the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest pharmacological activity. In stable renal transplant patients on cyclosporine based immunosuppression, approximately 28% of the oral mycophenolate sodium dose is converted to MPAG by pre-systemic metabolism. The half-life of MPAG is longer than MPA, approximately 15.7 (± 3.9) hours and its clearance is 0.45 (± 0.15) L/hr.

Elimination:

The majority of MPA (>60% of the dose) is eliminated in the urine primarily as MPAG and <3% as MPA. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6 - 8 hours after mycophenolate sodium dosing, a second peak of MPA concentration can be measured which is consistent with reabsorption of the deconjugated MPA.

Special Populations and Conditions

- **Pediatrics**: Safety and efficacy in children have not been established. Limited pharmacokinetics data are available on the use of mycophenolate sodium in children. Limited data are available at a dose of 450 mg/m^2 body surface area in children. The mean MPA pharmacokinetic parameters for stable pediatric renal transplant patients, 5 - 16 years, on cyclosporine are shown in Table 6. At the same dose administered based on body surface area, the respective mean C_{max} and AUC of MPA determined in children were higher by 33% and 18% than those determined for adults. The clinical impact of the increase in MPA exposure is not known.

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

- **Sex**: There are no significant gender differences in mycophenolate sodium pharmacokinetics.

- **Ethnic Origin:** Following a single dose administration of 720 mg mycophenolate sodium to 18 Japanese and Caucasian healthy subjects, the exposure (AUC_{inf}) for MPA and MPAG

were 15 and 22% lower in Japanese subjects compared to Caucasians. The peak concentrations (C_{max}) for MPAG were similar between the two populations, however, Japanese subjects had 9.6% higher C_{max} for MPA. These results do not suggest any clinically relevant differences.

- **Hepatic Insufficiency**: In a single dose (1 g MMF) 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 the 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 compared to healthy volunteers in other studies, thus making comparison between volunteers with alcoholic cirrhosis and health 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.

- **Renal Insufficiency**: No specific pharmacokinetic studies in individuals with renal impairment were conducted with mycophenolate sodium. MPA pharmacokinetic was unchanged over the range of normal to severely impaired renal function based on studies with mycophenolate mofetil. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria. Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the high plasma protein binding of MPA.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C - 30°C. Protect from moisture. Dispense in a tight container.

12 SPECIAL HANDLING INSTRUCTIONS

Tablets should not be crushed or cut.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

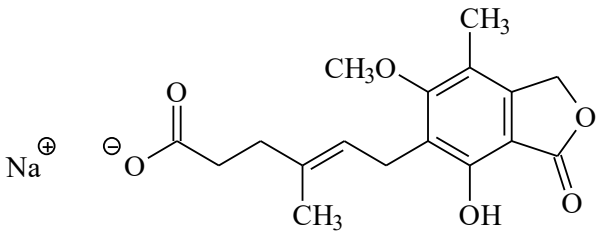
Drug Substance

Proper name: Mycophenolate Sodium

Chemical name: IUPAC: sodium (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydro-2-benzofuran-5-yl)-4-methylhex-4-enoate

Molecular formula and molecular mass: $C_{17}H_{19}NaO_6$; 342.32 g/mol

Structural formula:



Physicochemical properties:

Physical Description:	White to off-white powder
Solubility:	Soluble in water and methanol; sparingly soluble in acetone, butyl acetate, isopropanol, ether, methylene chloride and chloroform; insoluble in toluene and benzene.
Aqueous pH Solubility:	Highly soluble in aqueous media at physiological pH and practically insoluble in 0.1 N hydrochloric acid.
Partition Coefficient (Mycophenolic Acid):	Log P = 570 (octanol/phosphate buffer pH 2) Log P = 1.6 (octanol/phosphate buffer pH 7.4)
pKa Values (Mycophenolic Acid):	4.5 4.71 ± 0.10, 9.93 ± 0.20
pH:	7 to 8 (10% w/v solution in water at 21°C)
Melting Point:	189 to 190°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The safety and efficacy of mycophenolate sodium in combination with cyclosporine and corticosteroids for the prevention of organ rejection was assessed in two multicenter, randomized, double-blind trials in de novo and maintenance renal transplant patients compared to MMF.

14.2 Study Results

The *de novo* study was conducted in 423 renal transplant patients (ages 18 - 75 years) with the objective to confirm that mycophenolate sodium and MMF were therapeutically equivalent.

Patients were administered either mycophenolate sodium 1.44 g/day or MMF 2 g/day within 48 hours post-transplant for 12 months in combination with cyclosporine and corticosteroids. In the mycophenolate sodium and MMF groups, 39.4% and 42.9% respectively, received antibody therapy as an induction treatment. The primary efficacy endpoint was the incidence of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months. The incidence of biopsy-proven acute rejection, graft loss, death or loss to follow-up was similar in mycophenolate sodium and MMF-treated patients at 6 months, and met criteria confirming therapeutic equivalence, with similar results seen at 12 months (Table 7).

Table 7: Efficacy in *de novo* Renal Transplant Patients (Percent of Patients) at 6 and 12 Months of Treatment When Administered in Combination with Cyclosporine and Corticosteroids

Endpoints	Mycophenolate Sodium (N=213) n (%)	MMF (N=210) n (%)	Difference in event rate (Mycophenolate Sodium-MMF)	95% CI (Mycophenolate Sodium- MMF)
Primary efficacy endpoint at Month 6				
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	55 (25.8)	55 (26.2)	-0.4%	(-8.7%, 8.0%)
Biopsy-proven acute rejection	46 (21.6)	48 (22.9)	-1.3%	(-9.2%, 6.7%)
Graft loss or death	8 (3.8)	11 (5.2)	-1.5%	(-5.4%, 2.5%)
Graft loss	7 (3.3)	9 (4.3)	-1.0%	(-4.6%, 2.6%)
Death	1 (0.5)	2 (1.0)	-0.5%	--
Lost to follow-up[1]	3 (1.4)	0	1.4%	--

Endpoints	Mycophenolate Sodium (N=213) n (%)	MMF (N=210) n (%)	Difference in event rate (Mycophenolate Sodium-MMF)	95% CI (Mycophenolate Sodium- MMF)
Efficacy endpoints at Month 12				
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	61 (28.6)	59 (28.1)	0.5%	(-8.0%, 9.1%)
Graft loss, death or lost to follow-up	20 (9.4)	18 (8.6)	0.8%	(-4.6%, 6.3%)
Biopsy-proven acute rejection	48 (22.5)	51 (24.3)	-1.8%	(-9.8%, 6.3%)
Graft loss or death	11 (5.2)	14 (6.7)	-1.5%	(-6.0%, 3.0%)
Graft loss	9 (4.2)	9 (4.3)	-0.1%	(-3.9%, 3.8%)
Death	2 (0.9)	5 (2.4)	-1.4%	--
Lost to follow-up[1]	5 (2.3)	0	2.3%	--
[1] 'Lost to follow-up' endpoint calculated for the primary composite endpoint (biopsy-proven acute rejection, graft loss, death, or loss to follow-up).				

The maintenance study was conducted in 322 renal transplant patients (ages 18 - 75 years), who were at least 6 months post-transplant receiving 2 g/day MMF in combination with cyclosporine, with or without corticosteroids for at least four weeks prior to entry in the study. Patients were randomized to mycophenolate sodium 1.44 g/day or MMF 2 g/day for 12 months. The efficacy endpoint was the incidence of biopsy-proven acute rejection, graft loss, death, or loss to follow-up at 6 and 12 months. The rates of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 12 months were similar between mycophenolate sodium - and MMF-treated patients (Table 8).

Table 8: Efficacy in Maintenance Transplant Patients Parameters (Percent of Patients) at 6 and 12 Months of Treatment when Administered in Combination with Cyclosporine and with or without Corticosteroids

Endpoint	Months 0 to 6		Months 0 to 12	
	Mycophenolate Sodium (N=159) n (%)	MMF (N=163) n (%)	Mycophenolate Sodium (N=159) n (%)	MMF (N=163) n (%)
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	6 (3.8)	10 (6.1)	12 (7.5)	20 (12.3)

Endpoint	Months 0 to 6		Months 0 to 12	
	Mycophenolate Sodium (N=159) n (%)	MMF (N=163) n (%)	Mycophenolate Sodium (N=159) n (%)	MMF (N=163) n (%)
Biopsy-proven acute rejection, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	9 (5.7)	11 (6.7)	17 (10.7)	22 (13.5)
Graft loss, death or lost to follow-up	N/A	N/A	10 (6.3)	17 (10.4)
Biopsy-proven acute rejection	2 (1.3)	2 (1.2)	2 (1.3)	5 (3.1)
Acute rejection	2 (1.3)	3 (1.8)	2 (1.3)	6 (3.7)
Treated acute rejection	2 (1.3)	2 (1.2)	2 (1.3)	3 (1.8)
Acute rejections requiring antibody therapy	0	0	0	0
Biopsy-proven chronic rejection	4 (2.5)	4 (2.5)	6 (3.8)	8 (4.9)
Graft loss	0	1 (0.6)	0	1 (0.6)
Death[1]	0	1 (0.6)	2 (1.3)	4 (2.5)
Lost to follow-up[2]	4 (2.5)	6 (3.7)	8 (5.0)	12 (7.4)
Graft loss or death	0	2 (1.2)	2 (1.3)	5 (3.1)

[1] In addition, one patient (MMF group) withdrew consent on Day 273, and was discontinued from the study. Patient died post-study on Day 290. Patient was included in the composite variable as a 'lost to follow-up').

[2] 'Lost to follow-up' endpoint calculated for the primary composite endpoint (biopsy-proven acute rejection, graft loss, death, or lost to follow-up.

14.3 Comparative Bioavailability Studies

Fasting conditions

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study comparing Apo-Mycophenolic Acid 360 mg delayed-release tablets (Apotex Inc.) and Myfortic® 360 mg enteric-coated tablets (Novartis Pharmaceutics Canada Inc.), conducted under fasting conditions, was performed in healthy adult male and female subjects. A summary of the bioavailability data from the 24 subjects who completed the study is presented in the following table.

Table 1: Summary Table of the Comparative Bioavailability Data

Mycophenolic Acid (1 x 360 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	(%) Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	30945.64 32201.51 (32.87)	31430.55 32788.33 (32.21)	98.5	93.8-103.3
AUC_I (ng·h/mL)	31597.05 33920.27 (36.80)	32807.16 33269.98 (35.58)	96.3	91.0-101.9
C_{max} (ng/mL)	11399.68 12586.96 (37.89)	13906.69 15409.12 (43.90)	82.0	64.7-103.8
T_{max}[3] (h)	2.33 (1.33 – 12.00)	2.33 (1.33 – 5.00)		
T_{half}[4] (h)	12.84 (41.81)	11.60 (43.26)		

[1] Apo-Mycophenolic Acid (as mycophenolate sodium) delayed-release tablets, 360 mg (Apotex Inc.).

[2] Myfortic® (mycophenolic acid as mycophenolate sodium) enteric-coated tablets, 360 mg (Novartis Pharmaceuticals Canada Inc.).

[3] Expressed as the median (range).

[4] Expressed as arithmetic mean (CV%) only.

Fed conditions

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study comparing Apo-Mycophenolic Acid 360 mg delayed-release tablets (Apotex Inc.) and Myfortic® 360 mg enteric-coated tablets (Novartis Pharmaceutics Canada Inc.), conducted under high-fat, high-calorie fed conditions, was performed in healthy adult male and female subjects. A summary of the bioavailability data from the 16 subjects who completed the study is presented in the following table.

Table 2: Summary Table of the Comparative Bioavailability Data

Mycophenolic Acid (1 x 360 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	(%) Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	24988.91 26184.96 (32.36)	23637.75 25815.29 (47.03)	105.7	89.3-125.2
AUC_I (ng·h/mL)	27323.07 26818.13 (28.61)	21116.00 24994.12 (51.12)	129.4	93.9-178.3
C_{max} (ng/mL)	5821.01 7925.88 (78.44)	3665.42 5583.69 (88.82)	158.8	108.3-232.8

Mycophenolic Acid (1 x 360 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	(%) Ratio of Geometric Means	90% Confidence Interval
T_{max}[3] (h)	10.00 (4.00 – 16.00)	13.00 (4.00 – 24.00)		
T_{half}[4] (h)	13.69 (20.87)	14.48 (18.04)		

[1] Apo-Mycophenolic Acid (as mycophenolate sodium) delayed-release tablets, 360 mg (Apotex Inc.).

[2] Myfortic® (mycophenolic acid as mycophenolate sodium) enteric-coated tablets, 360 mg (Novartis Pharmaceuticals Canada Inc.).

[3] Expressed as the median (range).

[4] Expressed as arithmetic mean (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Animal toxicity and pharmacology

The hematopoetic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate sodium in rats and mice. Aplastic, regenerative anemia was identified as being the dose-limiting toxicity in rodents exposed to MPA. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) and a dose-dependent enlargement of the spleen and increase in extramedullary hematopoiesis. These effects occurred at systemic exposure levels which are equivalent to or less than the clinical exposure at the recommended dose of 1.44 g/day of mycophenolate sodium in renal transplant patients.

The nonclinical toxicity profile of mycophenolate sodium appears to be consistent with adverse events observed in humans exposed to MPA, which now provide safety data of more relevance to the patient population (see 8 ADVERSE REACTIONS). Single oral doses of MPA are moderately well tolerated in rats (LD_{50} of 350 - 700 mg/kg), well tolerated in mice or monkeys (LD_{50} of more than 1000 mg/kg), and extremely well tolerated in rabbits (LD_{50} of more than 6000 mg/kg).

Carcinogenicity: In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorigenic. The highest dose tested resulted in approximately 0.6 - 1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1.44g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 26-week oral carcinogenicity assay in a P53± (heterozygous)

transgenic mouse model, mycophenolate sodium at daily doses up to 200 mg/kg was not tumorigenic. The highest dose tested was 200 mg/kg, resulting in approximately 5 times the systemic exposure observed in renal transplant patients (1.44 g/day)

Genotoxicity: The genotoxic potential of mycophenolate sodium was determined in five assays. MPA was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay or the chromosomal aberration assay in human lymphocytes. The lowest dose showing genotoxic effects in a mouse bone marrow micronucleus resulted in approximately 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the tested clinical dose of 1.44 g of mycophenolate sodium per day. It is probable that the mutagenic activity observed was due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.

Reproductive and Developmental Toxicology: Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day. The systemic exposure at this dose represents approximately 9 times the clinical exposure at the tested clinical dose of 1.44 g of mycophenolate sodium per day. No effects on female fertility were seen up to a dose of 20 mg/kg/day, a dose at which maternal toxicity and embryotoxicity were already observed.

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day of mycophenolate sodium. In a pre- and postnatal development study in rat, mycophenolic acid (as sodium salt) caused developmental delays (abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg.

17 SUPPORTING PRODUCT MONOGRAPHS

1. MYFORTIC® Mycophenolic acid (as mycophenolate sodium) enteric-coated tablets, 180 mg and 360 mg, submission control 255453, Product Monograph, Novartis Pharmaceuticals Canada Inc. (JAN 24, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-MYCOPHENOLIC ACID

Mycophenolic Acid (as mycophenolate sodium) Delayed-Release Tablets

Read this carefully before you start taking **APO-MYCOPHENOLIC ACID** 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 **APO-MYCOPHENOLIC ACID.**

Serious Warnings and Precautions

- APO-MYCOPHENOLIC ACID will only be prescribed for you by a healthcare professional with experience in transplantation medicine.
- **Serious Immune System Problems:** APO-MYCOPHENOLIC ACID can have an effect on your immune system, which can lead to death. This can cause:
  - **Blood Problems:** APO-MYCOPHENOLIC ACID can cause serious blood problems. This includes; low levels of white blood cells that fight infections (**Leukopenia**), low levels of red blood cells (**Anemia**) and low levels of platelets, the cells that help the blood to clot (**Thrombocytopenia**).
  - **Progressive Multifocal Leukoencephalopathy:** An infection of the brain.
  - **Hepatitis B or C:** If you have had the liver disease hepatitis B or C in the past taking APO-MYCOPHENOLIC ACID might make it come back.
  - **Cancer:** APO-MYCOPHENOLIC ACID can increase your risk of developing certain types of cancer such as cancer of the lymph nodes (lymphoma) and skin cancer.
  - **Kidney Infection:** A viral infection of the kidneys.

  See the **Serious side effect and what to do about them** table, below for more information on these and other serious side effects.

- **Pregnancy:** Do **not** take APO-MYCOPHENOLIC ACID if you are pregnant. Taking APO-MYCOPHENOLIC ACID during pregnancy increases the risk of birth defects and pregnancy loss (miscarriage). If you are a woman who is able to get pregnant you must use two effective forms of birth control at the same time while you are taking APO-MYCOPHENOLIC ACID and for six weeks after your last dose.

What is APO-MYCOPHENOLIC ACID used for?

APO-MYCOPHENOLIC ACID is used in adults to suppress the immune system to prevent your body from rejecting a transplanted kidney.

How does APO-MYCOPHENOLIC ACID work?

Your body's immune system works to protect you from infections and other foreign material. When you receive a transplant, your immune system recognizes the new organ as "foreign", and will try to reject it. APO-MYCOPHENOLIC ACID works to suppress your immune system, so that your body is more likely to accept the transplanted kidney.

APO-MYCOPHENOLIC ACID is used together with other medicines containing cyclosporine and corticosteroids (e.g. prednisone, prednisolone, methyl prednisolone, prednisolone acetate, methyl prednisolone acetate) which also suppress your immune system. Together these drugs help prevent the rejection of your transplanted kidney.

What are the ingredients in APO-MYCOPHENOLIC ACID?

Medicinal ingredients: mycophenolate sodium

Non-medicinal ingredients: colloidal silicon dioxide, methycellulose, sodium lauryl sulfate, and stearic acid. The enteric coating of the tablet consists of hydroxypropyl methylcellulose, methacrylic acid copolymer, polyethylene glycol, talc, titanium dioxide, triethyl citrate, yellow iron oxide, FD&C Blue No. 2 (180 mg) and red iron oxide (360 mg).

APO-MYCOPHENOLIC ACID comes in the following dosage forms

Delayed-Release Tablets (coated to dissolve only in the intestine): 180 mg and 360 mg

Do not use APO-MYCOPHENOLIC ACID if:

- you are allergic (hypersensitive) to mycophenolic acid, mycophenolate sodium or mycophenolate mofetil or to any of the other ingredients of APO-MYCOPHENOLIC ACID.
- you are pregnant, planning to become pregnant or think you may be pregnant. APO-MYCOPHENOLIC ACID increases the risk of birth defects and pregnancy loss (miscarriage).
- you are a woman who is able to get pregnant and you are not using effective birth control.
- you are a woman who is able to get pregnant and you have not had two pregnancy tests to show that you are not pregnant.
- you are breast-feeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-MYCOPHENOLIC ACID. Talk about any health conditions or problems you may have, including if you:

- have or have had problems with your stomach (e.g. ulcers caused by the action of stomach acid) or digestive tract (e.g. ulcers, bleeding or perforation);

- need to receive any vaccines (especially live attenuated vaccines such as measles, mumps, rubella (MMR), rotavirus, chickenpox or yellow fever since vaccinations may be less effective during APO-MYCOPHENOLIC ACID treatment);

- have a family history of a genetic disease known as Lesch-Nyhan or Kelley-Seegmiller syndrome;

- have problems with your blood, such as low levels of white blood cells (leukopenia) or low levels of red blood cells (anemia).

Other warnings you should know about:

Donating Blood: You must not donate blood while you are taking APO-MYCOPHENOLIC ACID and for at least 6 weeks after you stop taking it.

Pregnancy, Birth Control and Breastfeeding:

Female Patients:

- Do **not** get pregnant while you are taking APO-MYCOPHENOLIC ACID and for 6 weeks after you stop taking it. APO-MYCOPHENOLIC ACID increases the risk of birth defects and pregnancy loss (miscarriage). Tell your healthcare professional immediately if you get pregnant while taking APO-MYCOPHENOLIC ACID. You will want to discuss the possible benefits and risks of continuing to take APO-MYCOPHENOLIC ACID.
- If you are a woman who is able to get pregnant, you must have two negative blood or urine pregnancy tests before you start taking APO-MYCOPHENOLIC ACID. The second test should be done 8-10 days after the first test and immediately before you start taking APO-MYCOPHENOLIC ACID. Your healthcare professional will also do pregnancy tests regularly during your treatment with APO-MYCOPHENOLIC ACID.
- If you are a woman who is able to get pregnant you must use two effective forms of birth control before you start taking APO-MYCOPHENOLIC ACID while you are taking it and for 6 weeks after you stop taking it. Talk to your healthcare professional about the birth control options that are right for you.
- You must **not** breastfeeding while you are taking APO-MYCOPHENOLIC ACID or for 6 weeks after you stop taking it. APO-MYCOPHENOLIC ACID may pass into breast milk and harm your baby.

Male Patients:

- You must **not** father a child while you are taking APO-MYCOPHENOLIC ACID or for 90 days after you stop taking it.
- You must use condoms if you are sexually active while you are taking APO-MYCOPHENOLIC ACID and for 90 days after you stop taking it.
- If your female partner is able to get pregnant she must use an effective form of birth control while you are taking APO-MYCOPHENOLIC ACID and for 90 days after you stop

taking it. Tell your healthcare professional immediately if your partner gets pregnant while you are taking APO-MYCOPHENOLIC ACID.
- You must not donate sperm/semen while you are taking APO-MYCOPHENOLIC ACID and for at least 90 days after you stop taking it.

Cancer Risk: APO-MYCOPHENOLIC ACID may increase your risk of developing certain types of cancer including cancer of the lymph nodes (lymphoma) and skin cancer. While you are taking APO-MYCOPHENOLIC ACID you should limit your exposure to sunlight and ultraviolet (UV) light by wearing appropriate protective clothing and frequently applying a sunscreen with a high protection factor.

Blood Tests and Monitoring: Be sure to keep all appointments at your transplant clinic. Your healthcare professional will do blood tests and other exams to monitor the levels of your red and white blood cells, the health of your liver and kidneys and to check for other side effects. You will need to have blood tests weekly during the first month, twice monthly for the second and third month of treatment, then monthly through the first year of treatment with APO-MYCOPHENOLIC ACID.

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 APO-MYCOPHENOLIC ACID:

- Medicines used to suppress the immune system other than cyclosporine or corticosteroids (e.g. azathioprine, mycophenolate mofetil, tacrolimus)
- Cholestyramine, (a medicine used to treat high blood cholesterol levels)
- Acyclovir (a medicine used to treat herpes infection)
- Gancyclovir (a medicine used to treat cytomegalovirus (CMV) infection)
- Antacids (used to treat heartburn)
- Oral birth control (also known as "The Pill")

How to take APO-MYCOPHENOLIC ACID:

- Do not break, crush, chew or cut APO-MYCOPHENOLIC ACID tablets. Do not take any tablets that are broken or split. The tablets should be swallowed whole with plenty of water.
- Space your two doses of APO-MYCOPHENOLIC ACID as evenly as you can throughout the day leaving about 12 hours between each dose.
- Try to take your doses at the same times each day. This will help keep a constant amount of medicine in your body so it can continue to protect your transplanted kidney. Taking your medicine at the same time each day will also help you remember each dose.
- APO-MYCOPHENOLIC ACID should be taken on an empty stomach, one hour before or two hours after food intake.

- Vomiting or diarrhea may prevent APO-MYCOPHENOLIC ACID from being taken up into your body. Always call your healthcare professional if you have vomiting or diarrhea.
- Your healthcare professional has decided on the dose of APO-MYCOPHENOLIC ACID you should take based on your medical condition and response to the medicine. Follow your healthcare professional's instructions carefully. Do not take any more or any less APO-MYCOPHENOLIC ACID than your healthcare professional has told you. Do not change the dose on your own, no matter how you are feeling.
- You will continue taking APO-MYCOPHENOLIC ACID for as long as you need immunosuppression to prevent you from rejecting your transplanted kidney.
- Talk to your healthcare professional about how to take your other immunosuppressant medicines while you are taking APO-MYCOPHENOLIC ACID

Usual dose:
Adults: 720 mg twice a day. This means:

-Taking 4 x 180 mg tablets in the morning and 4 x 180 mg tablets in the evening.

OR

-Taking 2 x 360 mg tablets in the morning and 2 x 360 mg tablets in the evening.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-MYCOPHENOLIC ACID, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Missing even a few doses of APO-MYCOPHENOLIC ACID may lead to rejection of your transplanted kidney. That is why it is so important to take each dose of APO-MYCOPHENOLIC ACID as prescribed.

If you have trouble remembering doses, or if you are uncertain about how to take them talk to your healthcare professional and be sure to discuss any concerns you have about taking APO-MYCOPHENOLIC ACID as prescribed.

If you forget to take APO-MYCOPHENOLIC ACID, take it as soon as you remember unless it is almost time for your next dose. Then take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose; Call your healthcare professional for advice if you are unsure. It is a good idea to ask your healthcare professional ahead of time what to do about missed doses.

Never allow your medication to run out between refills. Plan to order your refills about one week ahead of time. That way you will always have a supply in case the pharmacy is closed or

out of APO-MYCOPHENOLIC ACID. Also be sure to take enough medication with you when you go on a holiday.

What are possible side effects from using APO-MYCOPHENOLIC ACID?

These are not all the possible side effects you may have when taking APO-MYCOPHENOLIC ACID. If you experience any side effects not listed here, tell your healthcare professional.

Some effects could be serious:

If you experience any of the following while you are taking APO-MYCOPHENOLIC ACID, talk to your healthcare professional immediately:

- If you have symptoms of infection including fever, chills, sweating, fatigue, drowsiness, or lack of energy. Taking APO-MYCOPHENOLIC ACID you may be more susceptible to infections than usual. These may affect various body systems, the most common being the urinary tract, the respiratory tract and the skin.

- If you experience vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say, and muscle weakness, these can be the signs and symptoms of an infection of the brain called progressive multifocal leukoencephalopathy.

- If you have enlarged glands, new or enlarging skin growths, or a change in an existing mole. As can happen in patients taking immunosuppressive medication a very small number of APO-MYCOPHENOLIC ACID patients have developed cancer of the skin or lymph nodes.

- If you experience unusual tiredness, headache, shortness of breath with exercise or at rest, dizziness, chest pain, looking pale. These are all symptoms of anemia (low levels of red blood cells).

Other side effects may include:

Very common side effects *(> 1 in 10 patients).*

- diarrhea
- symptoms of infections including fever, sore throat, chills, sweating, fatigue, drowsiness, or lack of energy (low levels of white blood cells)
- muscle cramps (low levels of calcium in blood)
- muscle weakness, muscle spasms, abnormal heart rhythm (low levels of potassium in the blood)
  joint pain, stiffness, redness and swelling, especially of the big toe (high levels of uric acid in the blood) headache, dizziness (symptoms of high blood pressure)
- dizziness, light-headedness (symptoms of low blood pressure)

Common side effects *(≤ 10 in every 100 patients).*

- muscle cramps, muscle spasms, numbness and tingling in the hands and feet (low levels of magnesium in the blood)
- bleeding or bruising more easily than normal (low levels of blood platelets)
- muscle spasms, abnormal heart rhythm (high levels of potassium in the blood)
- excessive emotional distress, feeling troubled (anxiety)
- dizziness
- headache
- cough
- headache, dizziness, possibly with nausea (severe high blood pressure)
- shortness of breath, trouble breathing
- pain (e.g. in the abdomen, stomach, or joints)
- constipation
- indigestion
- flatulence
- loose stools
- nausea
- vomiting
- tiredness
- fever
- abnormal results of liver or kidney test
- joint pain
- weakness
- muscle pain
- swollen hands, ankles or feet (symptoms of edema)

Uncommon side effects *(<1 in 100 patients)*.

- cyst containing lymph fluid
- trouble sleeping
- shakiness, tremors
- lung congestion
- shortness of breath
- belching, bad breath
- bowel obstruction (inability to pass stool)
- inflammation of the esophagus
- bloody or black stools
- tongue discoloration
- dry mouth
- heartburn; inflammation of the gums
- inflammation of the lining of the abdominal cavity

- flu-like symptoms
- swelling of ankles and feet
- loss of appetite
- hair loss
- bruise of the skin
- acne
- fast heart beat; discharge of the eye with itching, redness and swelling
- blurred vision
- kidney problems (decreased urination, nausea, vomiting, swelling of extremities, fatigue)
- abnormal narrowing of the tube through which urine passes to the outside of the body
- cough, difficulty breathing, painful breathing (symptoms of lung disease including pulmonary fibrosis which can be fatal)

Other side effects with frequency not known
(Frequency cannot be estimated from the available data)

- rash
- fever, pain in joints, swelling of the joints (acute inflammatory syndrome)

Additional side effects have been reported with the class of drugs to which APO-MYCOPHENOLIC ACID belongs.

- inflammation of the colon or of the esophagus
- abdominal pain
- vomiting
- loss of appetite
- nausea
- inflammation of the pancreas (abdominal pain that lasts and gets worse when you lie down, nausea, vomiting)
- tear in the intestines
- stomach or intestine bleeding
- stomach pain with or without bloody or black stools
- bowel obstruction (inability to pass stool)
- serious infections
- low levels of specific white blood cells or of all blood cells
- fever, sore throat, frequent infections (symptoms of lack of white cells in the blood)

If any of these affects you, tell your healthcare professional. However, do not stop your medicines unless you have discussed this with your healthcare professional first.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Diarrhea	✓		
COMMON			
Bleeding or bruising more easily than normal		✓	
Pain: in the abdomen, stomach, or joints		✓	
Vomiting		✓	
Infections: fever, sore throat, chills, sweating, fatigue, drowsiness, lack of energy		✓	
Urinary tract infection: pain or burning when urinating, strong urge to urinate, cloudy or bloody urine, fever, chills		✓	
UNCOMMON			
Shortness of breath		✓	
Bloody or black stools		✓	
Swelling of ankles and feet		✓	
Palpitation or irregular heart beat		✓	
Viral Infections (cold sores and shingles)		✓	

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:

Store APO-MYCOPHENOLIC ACID tablets between 15°C to 30°C.

Protect from moisture.

Store APO-MYCOPHENOLIC ACID tablets in the original package.

Do not use APO-MYCOPHENOLIC ACID tablets after the expiry date printed on the container.

Keep out of the reach and sight of children.

If you want more information about APO-MYCOPHENOLIC ACID:

- 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); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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