PRODUCT MONOGRAPH

PrMYFORTIC®

Mycophenolic acid enteric-coated tablets 180 mg, 360 mg
(as mycophenolate sodium)
Novartis Standard

Immunosuppressant

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd., Dorval, Quebec
H9S 1A9

Date of Preparation:
February 14, 2005

Date of Revision:
May 10, 2018

Submission Control No: 214256

Table of Contents

PrMYFORTIC®

Mycophenolic acid enteric-coated tablets 180 mg, 360 mg
(as mycophenolate sodium), Novartis Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets, deliver the active moiety mycophenolic acid (MPA), an immunosuppressive agent.

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Enteric-Coated Tablets equivalent to mycophenolic acid 180 mg and 360 mg	lactose anhydrous.*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, and corticosteroids.

CONTRAINDICATIONS

- MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets are contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- MYFORTIC is contraindicated during pregnancy due to its mutagenic and teratogenic potential.

- MYFORTIC is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see WARNINGS and PRECAUTIONS).

- MYFORTIC should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.

- MYFORTIC is contraindicated in women who are breastfeeding.

WARNINGS AND PRECAUTIONS

Warning

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 MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets. 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 MYFORTIC during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

General

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

Vaccinations

During treatment with MYFORTIC, 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.

Infection

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 (MYFORTIC) 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 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 ADVERSE REACTIONS, Postmarketing Experience). 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 MYFORTIC and MMF. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Carcinogenesis

Patients receiving immunosuppressive regimens involving combinations of drugs, including MYFORTIC, 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.

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, MYFORTIC 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 MYFORTIC Enteric Coated Tablets during clinical trials. Most patients receiving MYFORTIC 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 MYFORTIC.

Drug Interactions

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

Hematologic

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MYFORTIC or mycophenolate mofetil (MMF) in combination with other immunosuppressive agents (see ADVERSE REACTIONS). The mechanism for MYFORTIC 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 MYFORTIC. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to MYFORTIC therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Patients receiving MYFORTIC should be monitored for blood dyscrasias (e.g. neutropenia or anemia) (see WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests). The development of neutropenia may be related to MYFORTIC itself, concomitant medications, viral infections, or some combination of these events. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count [ANC < $1.5\times10^3/\mu L$] or anemia), dosing with MYFORTIC should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION).

Inborn Disorders of Metabolism

On theoretical grounds, because MYFORTIC 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.

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 MYFORTIC 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 MYFORTIC than MMF. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (see DOSAGE AND ADMINISTRATION).

Sexual Function/Reproduction

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 MYFORTIC. No effects on female fertility were seen up to a dose of 20 mg/kg, 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.

Special Populations

Pregnant Women: MYFORTIC is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. MYFORTIC should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see CONTRAINDICATIONS and Post Market Adverse Drug Reactions). MYFORTIC 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 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 Post Market Adverse Drug Reactions).

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

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 MYFORTIC therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Prior to starting therapy with MYFORTIC, 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 8-10 days after the first one and immediately before starting MYFORTIC. 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 MYFORTIC (see DRUG INTERACTIONS). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

Nursing Women: MYFORTIC 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.

Additional precautions: 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.

Pediatrics: Safety and efficacy in pediatric patients have not been established. Limited pharmacokinetic data are available for pediatric renal transplant patients (see ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics: Patients ≥ 65 years may generally be at increased risk of adverse drug reactions due to an immunosuppression. Based on the controlled MYFORTIC clinical trials, patients > 65 receiving MYFORTIC 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.

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 < $1.3x10^3$ /µL) dosing with MYFORTIC should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (see WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

The incidence of adverse events for MYFORTIC Enteric-Coated Tablets 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 MYFORTIC or MMF in the 12-months

de novo renal study and maintenance renal study, when used in combination with cyclosporine are listed in Table 1. Adverse event rates were similar between MYFORTIC and MMF in both *de novo* and maintenance patients.

Table 1: Adverse Events (%) in Controlled *de novo* and Maintenance Renal Studies Reported in ≥ 10% of Patients

	***de novo* Renal Study**		**Maintenance Renal Study**	
	MYFORTIC 1.44 g/day (n=213)	**MMF 2 g/day (n=210)**	**MYFORTIC 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
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

Table 1: Adverse Events (%) in Controlled *de novo* and Maintenance Renal Studies Reported in ≥ 10% of Patients

	***de novo* Renal Study**		**Maintenance Renal Study**	
	MYFORTIC 1.44 g/day (n=213)	**MMF 2 g/day (n=210)**	**MYFORTIC 1.44 g/day (n=159)**	**MMF 2 g/day (n=163)**
Surgical and medical procedure				
Post-operative pain	23.9	18.6	-	-
Vascular disorder				
Hypertension	18.3	18.1	-	-

Table 2 summarizes the incidence of opportunistic infections in *de novo* and maintenance transplant patients, which were similar in both treatment groups.

Table 2: Viral and Fungal Infections (%) Reported Over 0-12 Months

	***de novo* Renal Study**		**Maintenance Renal Study**	
	MYFORTIC 1.44 g/day (n = 213)	**MMF 2 g/day (n = 210)**	**MYFORTIC 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 MYFORTIC (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 MYFORTIC in combination with cyclosporine and corticosteroids are listed in Table 3.

Table 3: Adverse Events Reported in 3% to <10% of Patients Treated with MYFORTIC 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	Abdominal pain, constipation,

	throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool	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
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 MYFORTIC 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 MYFORTIC, 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.

Post Market Adverse Drug Reactions

The postmarketing 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.

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.

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

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

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 MYFORTIC) in combination with other immunosuppressive agents (see WARNINGS AND PRECAUTIONS, Hematologic).

Musculoskeletal and connective tissue disorders: asthenia

Respiratory Disorders:
Bronchiectasis:
In transplant patients treated with MYFORTIC 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.

DRUG INTERACTIONS

Overview
MYFORTIC 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 MYFORTIC with other immunosuppressive agents have not been studied.

Drug-Drug Interactions

Table 4: Established or Predicted Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
Antacids/ Antacids with magnesium and aluminium hydroxides	Single-dose of MYFORTIC administered to 12 stable renal transplant patients alone and in combination with Maalox* (30 mL).	Absorption of a single dose of MYFORTIC 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 MYFORTIC 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 MYFORTIC 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 classes of antibiotics)	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
Cyclosporine	Stable renal transplant patients.	Cyclosporine pharmacokinetics were unaffected by steady-state dosing of MYFORTIC.	--
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 MYFORTIC and Gancyclovir are coadministered the dose recommendations for Gancyclovir should be observed and patients monitored carefully.

Table 4: Established or Predicted Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
Tacrolimus/ Neoral®	Calcineurin cross-over study in stable renal transplant patients	Mean MPA AUC was 19% higher and Cmax approximately 20% lower. Mean MPAG AUC and Cmax 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 MYFORTIC 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 MYFORTIC.
Oral contraceptives	CellCept* Prescribing Information.	None	Although not measured in a clinical trial, given the different metabolism of MYFORTIC and oral contraceptives, no drug interaction between these two classes of drug is expected, however, given that the long term effect of MYFORTIC dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected

Table 4: Established or Predicted Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
Proton Pump inhibitors	Clincal Expert report	In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of MYFORTIC and pantoprazole	

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

Drug-Food Interactions

Compared to the fasting state, administration of MYFORTIC 720mg 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, MYFORTIC should be taken on an empty stomach (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

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).

MYFORTIC (mycophenolic acid as mycophenolate sodium) Enteric-Coated Tablets should be used in combination with cyclosporine and corticosteroid therapy.

MYFORTIC should be taken on an empty stomach, one hour before or two hours after food intake (see Food Drug Interactions).

Patients are to be instructed that MYFORTIC 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.

Dose Adjustments

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 ACTION AND CLINICAL PHARMACOLOGY).

Treatment during Rejection Episodes: Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of MYFORTIC is not required.

Patients with Renal Impairment: No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. Patients with severe chronic renal impairment (GFR < 25 mL/min[1]/1.73 m^2) should be carefully followed.

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 /μL), dosing with MYFORTIC should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

For suspected drug overdose, contact your regional Poison Control Centre

There have been anecdotal reports of deliberate or accidental overdoses with MYFORTIC, 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 MYFORTIC could possibly result in oversuppression 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 103 / micro L or anaemia) it may be appropriate to interrupt or discontinue MYFORTIC (see Warnings and Precautions and 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 overdosage. 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.

ACTION AND CLINICAL PHARMACOLOGY

MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets, 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.

Pharmacokinetics

Table 5: Mean (±SD) Pharmacokinetic Parameters for MPA following Oral Administration of MYFORTIC to Renal Transplant Patients on cyclosporine Based Immunosuppression

Study Patient	MYFORTIC Dosing	N	Dose (mg)	T_{max}* (hr)	C_{max} (ug/ml)	AUC $_{0\text{-}12hr}$ (ug*hr/ml)
Adult	Single	24	720	2(0.8 - 8)	26.1±12.0	66.5 ±22.6**
Pediatric***	Single	10	450/m^2	2.5(1.5 - 24)	36.3± 20.9	74.3± 22.5**
Adult	Multiple x 6 days, BID	10	720	2(1.5 - 3.0)	37.0 ±13.3	67.9± 20.3
Adult	Multiple x 28 days, BID	36	720	2.5(1.5 - 8)	31.2± 18.1	71.2 ±26.3
Adult	Chronic, Multiple dose, BID					
	2 weeks post-transplant	12	720	1.8(1.0 - 5.3)	15.0 ±10.7	28.6 ±11.5
	3 months post-transplant	12	720	2(0.5 - 2.5)	26.2 ±12.7	52.3 ±17.4
	6 months post-transplant	12	720	2(0 - 3)	24.1± 9.6	57.2± 15.3
Adult	Chronic, Multiple dose, BID	18	720	1.5(0 - 6)	18.9 ±7.9	57.4± 15.0

* median (range), ** AUC0-8, *** age range of 5 - 16 years

The mean pharmacokinetic parameters for MPA following the administration of MYFORTIC in renal transplant patients on cyclosporine based immunosuppression are shown in Table 5. Single dose MYFORTIC 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 MYFORTIC (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 MYFORTIC Enteric Coated Tablet 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 MYFORTIC 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%. MYFORTIC pharmacokinetics is dose proportional over the dose range of 180 to 2160 mg.

Food effect: Compared to the fasting state, administration of MYFORTIC 720mg 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 (Cmax) of MPA, significant delays in absorption of MPA (Tmax delayed up to 20 hours) were observed. To avoid variations in MPA absorption between doses, MYFORTIC should be taken on an empty stomach (see DOSAGE AND ADMINISTRATION).

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 MYFORTIC 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 MYFORTIC dosing, a second peak of MPA concentration can be measured which is consistent with reabsorption of the deconjugated MPA.

Special Populations and Conditions

Ethnic groups/races

Following a single dose administration of 720 mg MYFORTIC to 18 Japanese and Caucasian healthy subjects, the exposure (AUCinf) for MPA and MPAG were 15 and 22% lower in Japanese subjects compared to Caucasians. The peak concentrations (Cmax) for MPAG were similar between the two populations, however, Japanese subjects had 9.6% higher Cmax for MPA. These results do not suggest any clinically relevant differences.

Pediatrics: Safety and efficacy in children have not been established. Limited pharmacokinetics data are available on the use of MYFORTIC 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 5. 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.

Geriatric: Pharmacokinetics in the elderly have not been formally studied.

Gender: There are no significant gender differences in MYFORTIC pharmacokinetics.

Hepatic Impairment: In a single dose (1g 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 Impairment: No specific pharmacokinetic studies in individuals with renal impairment were conducted with MYFORTIC. 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.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

Tablets should not be crushed or cut.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets are available in the following strengths which are equivalent to mycophenolic acid 180 mg and 360 mg:

180 mg Enteric-Coated tablet: Lime green film-coated round tablet with bevelled edges and the imprint (debossing) ‘C’ on one side, containing 180 mg mycophenolic acid as mycophenolate sodium. Provided in unit dose of 10 tablets/blister pack; 12 packs/carton.

360 mg Enteric-Coated tablet: Pale orange red film-coated ovaloid tablet with imprint (debossing) ‘CT’ on one side, containing 360 mg mycophenolic acid as mycophenolate sodium. Provided in unit dose of 10 tablets/blister pack; 12 packs/carton.

Each enteric-coated tablet also contains: colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. The enteric coating of the tablet consists of hypromellose phthalate, titanium dioxide, iron oxide yellow, and indigotine (180 mg enteric-coated tablet) or iron oxide red (360 mg enteric-coated tablet).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

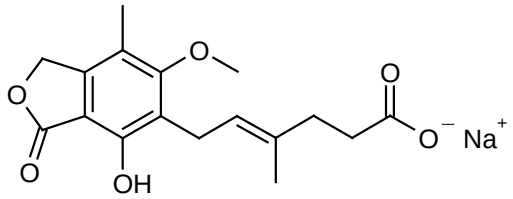
Proper name: mycophenolate sodium

Chemical name: (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt

Molecular formula: $C_{17}H_{19}O_6Na$

Molecular Weight: 342.32

Structural formula:



Physicochemical properties: *Physical Form*: White to off-white, crystalline powder
Solubility: Slightly soluble in aqueous media at physiological pH and practically insoluble in hydrochloric acid 0.1N

CLINICAL TRIALS The safety and efficacy of MYFORTIC (mycophenolate sodium) Enteric-Coated Tablets 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 .

Study Results

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

Patients were administered either MYFORTIC 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 MYFORTIC 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 MYFORTIC and MMF-treated patients at 6 months, and met criteria confirming therapeutic equivalence, with similar results seen at 12 months (Table 6).

Table 6: 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	MYFORTIC (N=213) n (%)	MMF (N=210) n (%)	Difference in event rate (MYFORTIC-MMF)	95% CI (MYFORTIC-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%	--
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 MYFORTIC 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 MYFORTIC and MMF-treated patients (Table 7).

Table 7: 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

	Months 0 to 6		Months 0 to 12	
Endpoint	**MYFORTIC (N=159) n (%)**	**MMF (N=163) n (%)**	**MYFORTIC (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)
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.

TOXICOLOGY

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9mg/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)

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 MYFORTIC 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.

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 MYFORTIC per day. No effects on female fertility were seen up to a dose of 20 mg/kg, a dose at which maternal toxicity and embryotoxicity were already observed.

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 MYFORTIC 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 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).

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1mg/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 MYFORTIC. 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.

REFERENCES

1. Heinschink A, Raab M, Daxecker H, et al. In vitro effects of mycophenolic acid on cell cycle and activation of human lymphocytes. Clin Chim Acta 2000; 300:23-8.

2. Johnson HJ et al. The pharmacokinetics of a single oral dose of mycophenolate mofetil in patients with varying degrees of renal function. Clin. Pharmacol Ther 1998; 63:512-518.

3. Parker G, et al. Pharmacokinetics of oral mycophenolate mofetil in volunteer subjects with varying degrees of hepatic oxidative impairment. J Clin Pharmacol 1996;36:332-44.

4. Lee HJ, Pawlak K, Nguyen BT, Bobins K and Sadee W. Biochemical differences among four inosinate dehydrogenase inhibitors, mycophenolic acid, ribavirin, tiazofurin, and selenazofurin, studied in mouse lymphoma cell culture. Cancer Research , 1985; 45:5512-5520.

5. Schmouder R, Arns W, Merkel F, et al. Pharmacokinetics of ERL080: A new enteric coated formulation of mycophenolic acid sodium. Transplantation 1999; 67(suppl):S203.

6. Weber LT, Shipkova M, Lamersdorf T, et al. Pharmacokinetics of mycophenolic acid (MPA) and determinants of MPA free fraction in pediatric and adult renal transplant recipients. J Am Soc Nephrol; 9:1511-1520.

7. Budde K, Curtis G, Knoll G,Chan L, Seifu Y, et al Enteric coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1 year study. Am J Transplant 2004; 4: 237 43.

8. Salvadori M., Holzer H, de Mattos A, Sollinger H, Arns W, Oppenheimer F, et al. Enteric coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in *de novo* renal transplant patients. Am J Transplant 2004; 4: 231 236

9. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ and Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006; 82 (12): 1698-1702.

PART III: CONSUMER INFORMATION

Pr**MYFORTIC®**
Mycophenolic acid enteric-coated tablets 180 mg, 360 mg
(as mycophenolate sodium), Novartis Standard

This leaflet is part III of a three-part "Product Monograph" published when MYFORTIC® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYFORTIC®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for: MYFORTIC is the brand name for a drug called mycophenolate sodium. MYFORTIC belongs to the class of drugs known as immunosuppressants. Immunosuppressants reduce your body's response to anything that it sees as "foreign" – which includes transplant organs.

What it does: MYFORTIC is used to prevent your body from rejecting a transplanted kidney.

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. MYFORTIC works to reduce this reaction, so that your body is more likely to accept the transplanted kidney.

MYFORTIC 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.

When it should not be used:

You should not take MYFORTIC if:
- you are allergic (hypersensitive) to mycophenolic acid, mycophenolate sodium or mycophenolate mofetil or to any of the other ingredients of MYFORTIC (see below).
- you are pregnant or planning to become pregnant or think you may be pregnant as mycophenolate causes birth defects and miscarriage
- you are a woman of childbearing potential not using effective contraception
- you are of childbearing potential and you have not had a pregnancy test to show that you are not pregnant
- you are breast-feeding

If any of the above apply to you, ask your doctor for advice.

What the medicinal ingredient is: MYFORTIC contains mycophenolate sodium, equivalent to 180 mg or 360 mg mycophenolic acid.

What the non-medicinal ingredients are: Colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. The enteric coating of the tablet consists of hypromellose phthalate, titanium dioxide, iron oxide yellow, and indigotine (180 mg tablets) or iron oxide red (360 mg tablets).

What dosage forms it comes in: MYFORTIC comes in the form of enteric-coated tablets (coated to dissolve only in the intestine).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- MYFORTIC may increase your risk of infection and development of cancer of the lymphoid tissues (called lymphoma) and other cancers.
- MYFORTIC will only be prescribed for you by a doctor with experience in transplantation medicine.
- Female users of childbearing potential must use contraception. Use of MYFORTIC during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

Follow your doctor's instructions carefully. They may differ from the general information contained in this leaflet.

- For Female Patients:

  - MYFORTIC causes fetal malformations and pregnancy loss including spontaneous abortion. Therefore, MYFORTIC must not be used in pregnant women. Should you become pregnant while on therapy with MYFORTIC, inform your doctor at once. You will want to discuss the possible benefits and risks of continuing with this drug.

  - Women of childbearing potential must have two negative serum (blood) or urine pregnancy tests; the second test, if possible, should be 8-10 days after the first one immediately before starting MYFORTIC.

  Effective contraception must be used before beginning MYFORTIC therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the patient should inform the physician immediately, and should discuss the potential risk to the fetus with him/her.

  -MYFORTIC must not be used while breast-feeding, or up to 6 weeks after you have stopped therapy. MYFORTIC may pass into breast milk and may harm your baby.

- MYFORTIC may reduce the effectiveness of vaccinations and the use of live attenuated vaccines should be avoided. Discuss it with your doctor before you get any vaccinations or

immunizations.

If you are a sexually active man, you must use condoms during treatment with MYFORTIC and for 90 days after stopping the treatment. Your partner should also use effective contraception during your treatment and for 90 days after you have stopped MYFORTIC. Tell your doctor straight away if your partner becomes pregnant while you are taking MYFORTIC.

Special precautions to be taken:

- Make sure you know if you are to stop, or to continue, the other immunosuppressant drugs you had been taking. Be sure to discuss this with your doctor.

- Exposure to sunlight should be limited. MYFORTIC reduces your body's defence mechanism, causing an increased risk of skin cancer. You should therefore limit your exposure to sunlight and ultraviolet (or UV) light by wearing appropriate protective clothing and frequently applying a sunscreen with a high protection factor.

- Be sure to keep all appointments at your transplant clinic. During these visits blood tests to determine the number of blood cells you have will need to be conducted weekly during the first month, twice monthly for the second and third month of treatment, then monthly through the first year. In addition, your doctor may order additional blood tests.

- If you already had hepatitis B or C MYFORTIC may increase the risk of these diseases re-appearing. Your doctor may perform blood analysis and check for symptoms of these diseases. If you experience any symptoms (yellow skin and eyes, nausea, loss of appetite, dark urine) you should inform your doctor immediately

BEFORE you use MYFORTIC talk to your doctor or pharmacist:

- if you are pregnant or are planning to become pregnant;

- if you are taking oral contraceptives;

- to ensure that you are using an appropriate method of contraception;

- if you are breast-feeding or plan to breast-feed;

- about all other medical conditions you have now or have had, including problems with your kidneys, stomach (e.g. ulcers caused by the action of stomach acid) or gastrointestinal tract (e.g. ulcers, bleeding, and perforation);

- if you need to receive vaccines (live attenuated vaccines);

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

- if you are allergic (hypersensitive) to mycophenolic acid, mycophenolate sodium or mycophenolate mofetil or to any of the other ingredients of MYFORTIC;

- if you have any diseases of the blood.

You must not donate blood during treatment with MYFORTIC and for at least 6 weeks after stopping treatment. Men must not donate sperm/semen during treatment with MYFORTIC and for at least 90 days after stopping treatment.

INTERACTIONS WITH THIS MEDICATION

- Tell all health professionals you see (doctors, dentists, nurses, pharmacists) that you are taking MYFORTIC.
- Do not take any other drugs without asking your doctor or pharmacist first. This includes anything you can buy off the shelf such as over-the-counter medicines (e.g. antacids) and natural health products.

Drugs that may interact with MYFORTIC include:
- Immunosuppressive agents 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).
- Non-prescription medications, including antacids or any natural health product.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose in adult is 720 mg administered twice daily. 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.

How it is taken:
- Do not break, crush, chew or cut MYFORTIC 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 MYFORTIC 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 drug in your body so it can

continue to protect your transplanted organ. Taking your medicine at the same time each day will also help you remember each dose.

- MYFORTIC should be taken on an empty stomach, one hour before or two hours after food intake.

- Vomiting or diarrhea may prevent MYFORTIC from being taken up into your body. Always call your doctor if you have either of these episodes.

- Your doctor has decided the dose of MYFORTIC you should take based on your medical condition and response to the drug. Follow your doctor's instruction carefully. Do not take any more or any less of the drug than your doctor has told you. Do not change the dose on your own, no matter how you are feeling.

How long is treatment continued:

- Treatment will continue for as long as you need immunosuppression to prevent you from rejecting your transplanted kidney.

Overdose:

In case of drug overdosage, contact a healthcare professional (e.g. doctor), hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

Missed Dose:

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

- If you have trouble remembering doses, or if you are uncertain about how to take them talk to your doctor, nurse or pharmacist and be sure to discuss any concerns you have about taking the drug as prescribed.

- If you ever do miss a dose of MYFORTIC, do not double dose or catch up on your own; instead call your doctor or pharmacist right away for advice. It is also a good idea to ask your doctor 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 the drug. Also be sure to take enough medication with you when you go on a holiday.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MYFORTIC can cause side effects, although not everybody gets them.

Some effects could be serious:

- If you have symptoms of infection including fever, chills, sweating, fatigue, drowsiness, or lack of energy. If you are taking MYFORTIC 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 MYFORTIC 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 anaemia (decrease in red blood cells).

If you experience any of these, tell your doctor straight away.

Other side effects may include:

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

- diarrhea
- low level of white blood cells
- reduced level of calcium in the blood , sometimes leading to cramps, (hypocalcemia)
- muscle weakness, muscle spasms, abnormal heart rhythm (possible symptoms of low level of potassium in the blood) (hypokalemia)
- abnormal blood test results (high level of uric acid in the blood) (hyperuricemia)
- headache, dizziness (possible symptoms of high blood pressure) (hypertension)
- dizziness, light-headedness (possible symptoms of low blood pressure) (hypotension)

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

- bleeding or bruising more easily than normal (signs of low level of blood platelets-thrombocytopenia)
- muscle spasms, abnormal heart rhythm (possible symptoms of high level of potassium in the blood) (hyperkalemia)
- abnormal blood test results (low level of magnesium in the blood) (hypomagnesemia)
- excessive emotional distress, troubled (symptoms of anxiety)
- dizziness
- headache
- cough
- headache, dizziness, possibly with nausea (possible symptoms of severe high blood pressure) (aggravated hypertension)
- shortness of breath, laborated breathing (possible symptoms of dyspnea or dyspnea exertional)

- 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
- pain in join (arthralgia)
- weakness (asthenia)
- muscle pain (myalgia)
- swollen hands, ankles or feet (possible symptoms of edema peripheral)

Uncommon side effects *(<1 in 100 patients).*
- cyst containing lymph fluid
- difficulty in sleeping
- shakiness
- lung congestion
- shortness of breath
- belching;bad breath
- bowel obstruction
- inflammation of the oesophagus
- 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
- vision blurred
- kidney disorders
- abnormal narrowing of the tube through which urine passes to the outside of the body
- cough, difficulty breathing, painful breathing (possible symptoms of interstitial lung disease including fatal pulmonary fibrosis)

Other side effect with frequency not known

(Frequency cannot be estimated from the available data)
- rash
- fever, sore throat, frequent infections (possible symptoms of lack of white cells in the blood) (agranulocytosis)

Additional side effects have been reported with the class of drugs to which MYFORTIC belongs.
- Inflammation of the colon or of the oesophagus
- abdominal pain
- vomiting
- loss of appetite
- nausea
- inflammation of the pancreas
- intestinal perforation
- stomach or intestine bleeding
- stomach pain with or without bloody or black stools
- bowel obstruction
- serious infections
- reduction in the number of specific white blood cells or of all blood cells

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist†
		Only if severe	In all cases	
Very common	Diarrhea	√		
Common	Bleeding or bruising more easily than normal; Pain (e.g. in the abdomen, stomach, or joints); Vomiting; Infections and symptoms of infection (e.g. fever, sore throat); Urinary tract infection		√	
Uncommon	Shortness of breath; Bloody or black stools; Swelling of ankles and feet; Palpitation or irregular heart beat; Viral Infections (cold sores and shingles)		√	

† Do not stop your medicines unless you have discussed this with your doctor first.

This is not a complete list of side effects. For any unexpected effects while taking MYFORTIC, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  -Mail to: Canada Vigilance Program
  Health Canada
  Post Locator 0701C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

• Store MYFORTIC between 15°C to 30°C.
• Protect from moisture.
• Store in the original package.
• Do not use MYFORTIC after the expiry date printed on the container.
• Keep out of the reach and sight of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.novartis.ca
or by contacting Novartis at:
1-800-363-8883
Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This leaflet was prepared by
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd., Dorval, Quebec
H9S 1A9

Last revised: May 10, 2018

MYFORTIC is a registered trademark.