

PRESCRIBING INFORMATION

PrMYFORTIC*

(mycophenolate sodium)

Enteric-Coated Tablets
equivalent to mycophenolic acid
180 mg and 360 mg

Immunosuppressant

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MYFORTIC is a registered trademark

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PrMYFORTIC*

(mycophenolate sodium)

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	colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

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).

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.

General

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

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

During treatment with MYFORTIC*, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil (MMF). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in MYFORTIC* and the active form of the drug. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies 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. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

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

Patients receiving MYFORTIC* should be monitored for neutropenia (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 neutropenia develops ($ANC < 1.3 \times 10^3 / \mu L$), 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 ($GFR < 25 \text{ mL/min/1.73 m}^2$) 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: 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 MYFORTIC*. In teratology studies in rabbits fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA). There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

There are no adequate and well-controlled studies in pregnant women conducted with either MYFORTIC* or mycophenolate mofetil. Based on data from the National Transplant Pregnancy Registry (NTPR), congenital disorders (congenital malformations of heart, ear, face, hand, eye, vertebrae, oesophagus, and multiple congenital abnormalities) have been reported in infants of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. The postmarketing data of pregnant women exposed to mycophenolate mofetil suggest that use of MPA during pregnancy may be associated with an increased risk of first trimester pregnancy loss. Mycophenolate mofetil is converted to mycophenolic acid following oral or IV administration. Since MPA may cause fetal harm when administered to a pregnant woman, MYFORTIC* should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that MYFORTIC* therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

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 (see CONSUMER INFORMATION).

Nursing Women: It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from mycophenolate sodium, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the

mother.

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 ($ANC < 1.3 \times 10^3 / \mu L$) 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 ($\geq 25\%$) 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 ($\geq 15\%$). Fatal infections were rarely observed in patients receiving MYFORTIC* (0.5%) in controlled clinical trials.

The incidence of adverse events for MYFORTIC* (mycophenolate sodium) 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 $\geq 10\%$ 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 $\geq 10\%$ of Patients

	<i>de novo</i> 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
Surgical and medical procedure				
Post-operative pain	23.9	18.6	-	-
Vascular disorder				

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

	<i>de novo</i> 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)
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

	<i>de novo</i> 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	21.6	20.5	1.9	1.8
- Cytomegalovirus disease	4.7	4.3	0	0.6
Herpes simplex	8	6.2	1.3	2.5
Herpes zoster	4.7	3.8	1.9	3.1
Any fungal infection	10.8	11.9	2.5	1.8
- Candida NOS	5.6	6.2	0	1.8
- Candida albicans	2.3	3.8	0.6	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

	<i>de novo</i> 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
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

Based on data from the National Transplant Pregnancy Registry (NTPR), congenital disorders (congenital malformations of heart, ear, face, hand, eye, vertebrae, oesophagus, and multiple congenital abnormalities) have been reported in infants of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. The postmarketing data of pregnant women exposed to mycophenolate mofetil suggest that use of MPA during pregnancy may be associated with an increased risk of first trimester pregnancy loss. (see WARNINGS AND PRECAUTIONS, Special Populations).

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil (MMF). Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in MYFORTIC* and the active form of the drug (see WARNINGS AND PRECAUTIONS, General).

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	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.
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.
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	--

Table 4: Established or Predicted Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
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.

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 ($\text{GFR} < 25 \text{ mL/min}^1/1.73 \text{ m}^2$) 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 ($\text{ANC} < 1.3 \times 10^3 /\mu\text{L}$), dosing with MYFORTIC* should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

There has been no reported experience of acute overdose of MYFORTIC* (mycophenolate sodium) Enteric-Coated Tablets in humans.

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

Distribution: The volume of distribution at steady-state for MPA is 54.3 (\pm 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 (\pm 3.2) hours and the clearance is 8.4 (\pm 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 (\pm 3.9) hours and its clearance is 0.45 (\pm 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

Pediatrics: Limited data are available on the use of MYFORTIC* at a dose of 450 mg/m² 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 Insufficiency: 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 Insufficiency: 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.

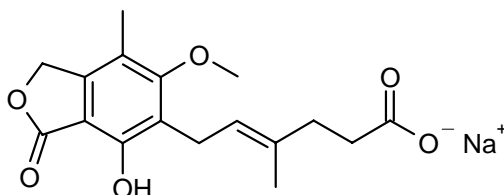
Each enteric-coated tablet also contains: colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. The enteric coating of the tablet consists of hypromellose phthalate, titanium dioxide, iron oxide yellow, and indigotine (180 mg enteric-coated tablet) 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 ₆ Na
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	MYFORTI C* (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 8).

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

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

¹In 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

The hematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate sodium in rats and mice. 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).

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.

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*.

Single oral doses of MPA are moderately well tolerated in rats (LD₅₀ of 350-700 mg/kg), well tolerated in mice or monkeys (LD₅₀ of more than 1000 mg/kg), and extremely well tolerated in rabbits (LD₅₀ of more than 6000 mg/kg).

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.

There are no relevant qualitative or quantitative differences in the genotoxic potential of mycophenolate sodium and mycophenolate mofetil. 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. These effects can be related to the pharmacodynamic mode of action of MPA through its inhibition of nucleotide synthesis in sensitive cells.

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).

REFERENCES

1. Manuscript (Study ERLB 301): Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in *de novo* renal transplant patients.
2. Manuscript (Study ERLB 302): Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. B302 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.
10. B301 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
11. 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.

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