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Myfortic® (mycophenolic acid) delayed-release tablets 180 mg and 360 mg

US Package Insert

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TRADEMARK

MYFORTIC® (mycophenolic acid) delayed-release tablets

Rx only

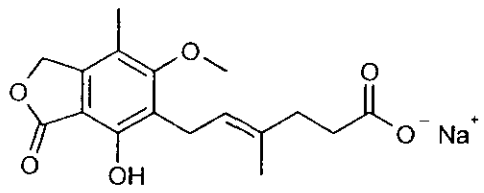
Prescribing Information

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 organ transplant recipients should use Myfortic. Patients receiving Myfortic 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.

DESCRIPTION

Myfortic® (mycophenolic acid) delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid (MPA). Myfortic is an immunosuppressive agent. As the sodium salt, MPA is chemically designated as (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt.

Its empirical formula is $C_{17}H_{19}O_6$ Na. The molecular weight is 342.32 and the structural formula is



Myfortic, as the sodium salt, is a white to off-white, crystalline powder and is highly soluble in aqueous media at physiological pH and practically insoluble in 0.1 N hydrochloric acid.

Myfortic is available for oral use as delayed-release tablets containing either 180 mg or 360 mg of mycophenolic acid. Inactive ingredients include 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) or iron oxide red (360 mg).

CLINICAL PHARMACOLOGY

Mechanism of Action

MPA is an 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 potent cytostatic effect on lymphocytes.

Mycophenolate sodium has been shown to prevent the occurrence of acute rejection in rat models of kidney and heart allotransplantation. Mycophenolate sodium also decreases antibody production in mice.

Pharmacokinetics

Absorption

In vitro studies demonstrated that the enteric coated Myfortic 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 in several pharmacokinetic studies conducted in renal transplant patients, consistent with its enteric-coated formulation, the median delay (T_{lag}) in the rise of MPA concentration ranged between 0.25 and 1.25 hours and the median time to maximum concentration (T_{max}) of MPA ranged between 1.5 and 2.75 hours. In comparison, following the administration of mycophenolate mofetil, the median T_{max} ranged between 0.5 and 1.0 hours. In stable renal transplant patients on cyclosporine, USP (MODIFIED) based immunosuppression, gastrointestinal absorption and absolute bioavailability of MPA following the administration of Myfortic delayed-release tablet was 93% and 72%, respectively. Myfortic pharmacokinetics is dose proportional over the dose range of 360 to 2160 mg.

Distribution

The mean (± SD) volume of distribution at steady-state and elimination phase for MPA is 54 (± 25) L and 112 (± 48) L, respectively. 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).

Metabolism

MPA is metabolized principally by glucuronyl transferase to glucuronidated metabolites. The phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG), is the predominant metabolite of MPA and does not manifest pharmacological activity. The acyl glucuronide is a minor metabolite and has comparable pharmacological activity to MPA. In stable renal transplant patients on cyclosporine, USP (MODIFIED) based immunosuppression, approximately 28% of the oral Myfortic dose was converted to MPAG by pre-systemic metabolism. The AUC ratio of MPA:MPAG:acyl glucuronide is approximately 1:24:0.28 at steady state. The mean clearance of MPA was 140 (± 30) mL/min.

Elimination

The majority of MPA dose administered is eliminated in the urine primarily as MPAG (>60%) and approximately 3% as unchanged MPA following Myfortic administration to stable renal transplant patients. The mean renal clearance of MPAG was 15.5 (± 5.9)

mL/min. MPAG is also secreted in the bile and available for deconjugation by gut flora. MPA resulting from the deconjugation may then be reabsorbed and produce a second peak of MPA approximately 6 – 8 hours after Myfortic dosing. The mean elimination half-life of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.

Food Effect

Compared to the fasting state, administration of Myfortic 720 mg with a high fat meal (55g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA. However, there was a 33% decrease in the maximal concentration (C_{max}), a 3.5-hr delay in the T_{lag} (range, -6 to 18 hr), and 5.0-hr delay in the T_{max} (range, -9 to 20 hr) of MPA. To avoid the variability in MPA absorption between doses, Myfortic should be taken on an empty stomach. (see DOSAGE AND ADMINISTRATION and PRECAUTIONS: Information for Patients)

Pharmacokinetics in Renal Transplant Patients

The mean pharmacokinetic parameters for MPA following the administration of Myfortic in renal transplant patients on cyclosporine, USP (MODIFIED) based immunosuppression are shown in Table 1. Single dose Myfortic pharmacokinetics predicts multiple dose pharmacokinetics. However, in the early post transplant period, mean MPA AUC and Cmax were approximately one-half of those measured six months post transplant.

After near equimolar dosing of Myfortic 720 mg BID and mycophenolate mofetil 1000 mg BID (739 mg as MPA) in both the single and multiple dose cross-over trials, mean systemic MPA exposure (AUC) was similar.

Table 1 Mean ± SD Pharmacokinetic Parameters for MPA following the Oral Administration of Myfortic to Renal Transplant Patients on Cyclosporine, USP (MODIFIED) Based Immunosuppression

Study Patient	Myfortic Dosing	n	Dose (mg)	T_{max}* (hr)	C_{max} (µg/ml)	$AUC_{0\text{-}12hr}$ (µg*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), ** $AUC_{0-\infty}$, *** age range of 5 – 16 years

Special Populations

Renal Insufficiency: No specific pharmacokinetic studies in individuals with renal impairment were conducted with Myfortic. However, based on studies of renal impairment with mycophenolate mofetil, MPA exposure is not expected to be appreciably increased over the range of normal to severely-impaired renal function following Myfortic administration. In contrast, MPAG exposure would be increased markedly 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.

Hepatic Insufficiency: No specific pharmacokinetic studies in individuals with hepatic impairment were conducted with Myfortic. In a single dose (mycophenolate mofetil 1000 mg) 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, such as primary biliary cirrhosis, with other etiologies may show a different effect.

Pediatrics: Limited data are available on the use of Myfortic 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, USP (MODIFIED) are shown in Table 1. 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.

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

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

CLINICAL STUDIES

The safety and efficacy of Myfortic in combination with cyclosporine, USP (MODIFIED) 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 mycophenolate mofetil.

The *de novo* study was conducted in 423 renal transplant patients (ages 18-75 years) in Austria, Canada, Germany, Hungary, Italy, Norway, Spain, UK and USA. Cadaveric donor specimens accounted for 84% of randomized patients. Patients were administered either Myfortic 1.44 g/day or mycophenolate mofetil 2 g/day within 48 hours post-transplant for 12 months in combination with cyclosporine, USP (MODIFIED) and corticosteroids. Forty-one percent of patients received antibody therapy as induction treatment. Treatment failure was defined as the first occurrence of biopsy-proven acute rejection, graft loss, death or loss to

follow-up at 6 months. The incidence of treatment failure was similar in Myfortic- and mycophenolate mofetil-treated patients at 6 and 12 months (Table 2). The cumulative incidence of graft loss, death and lost to follow-up at 12 months is also given in Table 2.

Table 2 Treatment failure in *de novo* Renal Transplant Patients (Percent of Patients) at 6- and 12-Months of Treatment When Administered in Combination with Cyclosporine* and Corticosteroids

	Myfortic 1.44 g/day (n=213)	**mycophenolate mofetil 2 g/day (n=210)**
6 months	**n (%)**	**n (%)**
Treatment failure#	55 (25.8)	55 (26.2)
Biopsy-proven acute rejection	46 (21.6)	48 (22.9)
Graft loss	7 (3.3)	9 (4.3)
Death	1 (0.5)	2 (1.0)
Lost to follow-up**	3 (1.4)	0
12 months	**n (%)**	**n (%)**
Graft loss or death or lost to follow-up***	20 (9.4)	18 (8.6)
Treatment failure	61 (28.6)	59 (28.1)
Biopsy-proven acute rejection	48 (22.5)	51 (24.3)
Graft loss	9 (4.2)	9 (4.3)
Death	2 (0.9)	5 (2.4)
Lost to follow-up**	5 (2.3)	0

*USP (MODIFIED)

**Lost to follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death

***Lost to follow-up indicates patients who were lost to follow-up without prior graft loss or death (9 Myfortic patients and 4 mycophenolate mofetil patients)

#95% confidence interval of the difference in treatment failure at 6 months (Myfortic – mycophenolate mofetil) is (-8.7%, 8.0%).

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 mycophenolate mofetil in combination with cyclosporine USP (MODIFIED), with or without corticosteroids for at least two weeks prior to entry in the study. Patients were randomized to Myfortic 1.44 g/day or mycophenolate mofetil 2 g/day for 12 months. The study was conducted in Austria, Belgium, Canada, Germany, Italy, Spain, and USA. Treatment failure was defined as the first occurrence of biopsy-proven acute rejection, graft loss, death, or loss to follow-up at 6 and 12 months. The incidences of treatment failure at 6 and 12 months were similar between Myfortic- and mycophenolate mofetil-treated patients (Table 3). The cumulative incidence of graft loss, death and lost to follow-up at 12 months is also given in Table 3.

Table 3 Treatment Failure in Maintenance Transplant Patients (Percent of Patients) at 6- and 12-Months of Treatment when Administered in Combination with Cyclosporine* and with or without Corticosteroids

	Myfortic 1.44 g/day (n = 159)	**mycophenolate mofetil 2 g/day (n = 163)**

	Myfortic 1.44 g/day (n = 159)	mycophenolate mofetil 2 g/day (n = 163)
6 months	**n (%)**	**n (%)**
Treatment failure#	7 (4.4)	11 (6.7)
Biopsy-proven acute rejection	2 (1.3)	2 (1.2)
Graft loss	0	1 (0.6)
Death	0	1 (0.6)
Lost to follow-up**	5 (3.1)	7 (4.3)
12 months	**n (%)**	**n (%)**
Graft loss or death or lost to follow-up***	10 (6.3)	17 (10.4)
Treatment failure	12 (7.5)	20 (12.3)
Biopsy-proven acute rejection	2 (1.3)	5 (3.1)
Graft loss	0	1 (0.6)
Death	2 (1.3)	4 (2.5)
Lost to follow-up**	8 (5.0)	10 (6.1)

* USP (MODIFIED)

**Lost to follow-up indicates patients who were lost to follow-up without prior biopsy-proven acute rejection, graft loss, or death

***Lost to follow-up indicates patients who were lost to follow-up without prior graft loss or death (8 Myfortic patients and 12 mycophenolate mofetil patients)

#95% confidence interval of the difference in treatment failure at 6 months (Myfortic – mycophenolate mofetil) is (-7.4%, 2.7%).

The safety and efficacy of Myfortic has not been studied in hepatic or cardiac transplant trials.

INDICATIONS AND USAGE

Myfortic (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

CONTRAINDICATIONS

Myfortic is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients.

WARNINGS (see boxed WARNING)

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Fatal infections can occur in patients receiving immunosuppressive therapy. (see ADVERSE REACTIONS)

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, cyclosporine, and corticosteroids. The efficacy and safety of Myfortic in combination with other immunosuppression agents have not been determined.

The rates for lymphoproliferative disease or lymphoma in Myfortic treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies. (see ADVERSE REACTIONS)

There are no adequate and well-controlled studies in pregnant women conducted with MPA, Myfortic, or mycophenolate mofetil. 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 physician and patient should discuss the potential risk to the fetus. (see PRECAUTIONS: Pregnancy and Information for Patients)

Patients receiving Myfortic should be monitored for neutropenia (see PRECAUTIONS: 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 < 1.3×10^3 /μL), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. (see DOSAGE AND ADMINISTRATION)

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

Precautions

General

Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with Myfortic (up to 12 months). Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed. 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. Because MPA 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. (See ADVERSE REACTIONS)

Subjects with severe chronic renal impairment (GFR < 25 mL/min/1.73 m^2) may present higher plasma MPA and 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 mycophenolate mofetil group experienced delayed graft function (DGF). Although patients with DGF experienced a higher incidence of certain adverse events (anemia, leukopenia, and hyperkalemia) than patients without DGF, these events in DGF patients were not more frequent in patients receiving Myfortic compared to mycophenolate mofetil. No dose adjustment is recommended for these patients; however, such patients should be carefully observed. (see CLINICAL PHARMACOLOGY: DOSAGE AND ADMINISTRATION)

In view of the significant reduction in the AUC of MPA by cholestyramine when administered with mycophenolate mofetil, 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. (see PRECAUTIONS: Drug Interactions)

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.

During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. (see PRECAUTIONS: Drug Interactions: Live Vaccines)

Information for Patients

It is recommended that Myfortic be administered on an empty stomach, one hour before or two hours after food intake. (see DOSAGE AND ADMINISTRATION)

In order to maintain the integrity of the enteric coating of the tablet, patients should be instructed not to crush, chew, or cut Myfortic tablets and to swallow the tablets whole. Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Myfortic. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies.

Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning Myfortic therapy, during therapy, and for 6 weeks after Myfortic has been stopped. (see WARNINGS and PRECAUTIONS: Pregnancy)

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)

Drug Interactions

The following drug interaction studies have been conducted with Myfortic:

Antacids: Absorption of a single dose of Myfortic was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum containing antacids (30 mL): the mean C_{max} and $AUC_{(0-t)}$ values for MPA were 25% and 37% lower, respectively, than when Myfortic was administered alone under fasting conditions. It is recommended that Myfortic and antacids not be administered simultaneously.

Cyclosporine: When studied in stable renal transplant patients, cyclosporine, USP (MODIFIED) pharmacokinetics were unaffected by steady-state dosing of Myfortic.

The following recommendations are derived from drug interaction studies conducted following the administration of mycophenolate mofetil:

Acyclovir/Ganciclovir: may be taken with Myfortic; however, during the period of treatment, physicians should monitor blood cell counts. Both acyclovir/ganciclovir and MPAG concentrations are increased in the presence of renal impairment, their coexistence may compete for tubular secretion and further increase in the concentrations of the two.

Azathioprine/mycophenolate mofetil: 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: These drugs interrupt enterohepatic recirculation and reduce MPA exposure when coadministered with mycophenolate mofetil. Therefore, do not administer Myfortic with cholestyramine or other agents that may interfere with entrohepatic recirculation or drugs 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: Given the different metabolism of Myfortic and oral contraceptives, no drug interaction between these two classes of drug is expected. However, in a drug-drug interaction study, mean levonorgesterol AUC was decreased by 15% when coadministered with mycophenolate mofetil. Therefore, it is recommended that oral contraceptives are co-administered with Myfortic with caution and additional birth control methods be considered. (see PRECAUTIONS: Pregnancy)

Live vaccines: During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination. (see PRECAUTIONS: General)

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6-times the proposed mycophenolate sodium therapeutic dose based upon body surface area).

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium 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 (*Salmonella typhimurium* TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately two-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily dose of 20 mg/kg, which was approximately three-fold higher than the recommended therapeutic dose based upon systemic exposure.

Pregnancy Category C

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, Myfortic should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus.

It is recommended that Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their physician immediately should pregnancy occur.

Effective contraception must be used before beginning Myfortic therapy, during therapy, and for six weeks following discontinuation of therapy. (see WARNINGS)

Nursing Mothers

It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MPA, 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.

Pediatric Use

De novo renal transplant

The safety and effectiveness of Myfortic in *de novo* pediatric renal transplant patients have not been established.

Stable renal transplant

There are no pharmacokinetic data available for pediatric patients <5 years. The safety and effectiveness of Myfortic have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic in this age group is supported by evidence from adequate and well-controlled studies of Myfortic in stable adult renal transplant patients. Limited pharmacokinetic data are available for stable pediatric renal transplant patients in the age group 5-16 years. Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets. (see CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION)

Geriatric Use

Patients ≥ 65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The incidence of adverse events for Myfortic 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.

The principal adverse reactions associated with the administration of Myfortic include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

Adverse events reported in ≥ 20% of patients receiving Myfortic or mycophenolate mofetil in the 12-months *de novo* renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids are listed in Table 4. Adverse event rates were similar between Myfortic and mycophenolate mofetil in both *de novo* and maintenance patients.

Table 4 Adverse Events (%) in Controlled *de novo* and Maintenance Renal Studies Reported in ≥ 20% of Patients

	de novo Renal Study		Maintenance Renal Study	
	Myfortic 1.44 g/day (n=213)	**mycophenolate mofetil 2 g/day (n=210)**	**Myfortic 1.44 g/day (n=159)**	**mycophenolate mofetil 2 g/day (n=163)**
Blood and lymphatic system disorders				
Anemia	21.6	21.9	–	–
Leukopenia	19.2	20.5	–	–
Gastrointestinal system disorders				
Constipation	38.0	39.5	–	–
Nausea	29.1	27.1	24.5	19
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23.0	20.0	–	–
Dyspepsia	22.5	19.0	–	–
Infections and infestations				
Urinary tract infection	29.1	33.3	–	–
CMV infection	20.2	18.1	–	–
Nervous system disorder				
Insomnia	23.5	23.8	–	–
Surgical and medical procedure				
Post-operative pain	23.9	18.6	–	–

Table 5 summarizes the incidence of opportunistic infections in *de novo* and maintenance transplant patients, which were similar in both treatment groups.

Table 5 Viral and Fungal Infections (%) Reported Over 0-12 Months

	de novo Renal Study		Maintenance Renal Study	
	Myfortic 1.44 g/day (n = 213)	**mycophenolate mofetil 2 g/day (n = 210)**	**Myfortic 1.44 g/day (n = 159)**	**mycophenolate mofetil 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	8.0	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

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.

The following adverse events were reported between 3% to < 20% incidence in *de novo* and maintenance patients treated with Myfortic in combination with cyclosporine and corticosteroids are listed in Table 6.

Table 6 Adverse Events Reported in 3% to < 20% 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	Abdominal pain upper, Flatulence, abdominal distension, sore throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool	Vomiting, dyspepsia, Abdominal pain, constipation, gastroesophageal reflux disease, loose stool, flatulence, abdominal pain upper
General disorders and administration site conditions	Edema, edema lower limb, pyrexia, pain, fatigue, edema peripheral, chest pain	Fatigue, pyrexia, edema, chest pain, peripheral edema
Infections and infestations	Nasopharyngitis, herpes simplex, upper respiratory tract infection, oral candidiasis, herpes zoster, sinusitis, wound infection, implant infection, pneumonia	Nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza, sinusitis
Injury, poisoning, and procedural complications	Drug toxicity	Post procedural pain
Investigations	Blood creatinine increased Hemoglobin decrease, blood	Blood creatinine increase, weight increase

	pressure increased, liver function tests abnormal	
Metabolism and nutrition disorders	Hypocalcemia, hyperuricemia, hyperlipidemia, hypokalemia, hypophospahtemia Hypercholesterolemia, hyperkaliemia, hypomagnesemia, diabetes mellitus, hyperphosphatemia, dehydration, fluid overload, hyperglycemia, hypercalcemia	Dehydration, hypokalemia, hypercholesterolemia
Musculoskeletal and connective tissue disorders	Back pain, arthralgia, pain in limb, muscle cramps, myalgia	Arthralgia, pain in limb, back pain, muscle cramps, peripheral swelling, myalgia
Nervous system disorders	Tremor, headache, dizziness (excluding vertigo)	Headache, 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	Cough, 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, hypertension aggravated, hypotension	Hypertension

* USP (MODIFIED)

The following additional adverse reactions have been associated with the exposure to MPA when administered as a sodium salt or as mofetil ester:

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

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

Respiratory: interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely with MPA administration and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post transplant patients receiving MPA derivatives.

OVERDOSAGE

Signs and Symptoms

There has been no reported experience of acute overdose of Myfortic 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.

Treatment and Management

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.

DOSAGE AND ADMINISTRATION

The recommended dose of Myfortic is 720 mg administered twice daily (1440 mg total daily dose) on an empty stomach, one hour before or two hours after food intake (see CLINICAL PHARMACOLOGY: Food Effect).

Myfortic delayed-release tablets and mycophenolate mofetil tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent

Patients are to be instructed that Myfortic tablets should not be crushed, chewed, or cut prior to ingesting. The tablets should be swallowed whole in order to maintain the integrity of the enteric coating.

Pediatric: Based on a pharmacokinetic study conducted in stable renal pediatric transplant patients, the recommended dose of Myfortic in stable pediatric patients is 400 mg/m^2 body surface area (BSA) administered twice daily (up to a maximum dose of 720 mg administered twice daily). Patients with a BSA of 1.19 to 1.58 m^2 may be dosed either with three Myfortic 180 mg tablets or one 180 mg tablet plus one 360 mg tablet twice daily (1080 mg daily dose). Patients with a BSA of > 1.58 m^2 may be dosed either with four Myfortic 180 mg tablets or two Myfortic 360 mg tablets twice daily (1440 mg daily dose). Pediatric doses for patients with BSA < 1.19 m^2 cannot be accurately administered using currently available formulations of Myfortic tablets.

Geriatrics: The maximum recommended dose is 720 mg administered twice daily.

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/1.73 m^2 BSA) should be carefully followed for potential adverse reactions due to increase in free MPA and total MPAG concentrations. (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations)

Patients with hepatic impairment

No dose adjustments are needed for renal transplant patients with hepatic parenchymal disease. However, it is not known whether dosage adjustments are needed for hepatic disease with other etiologies. (see CLINICAL PHARMACOLOGY: Pharmacokinetics)

How Supplied

Myfortic® (mycophenolic acid) delayed-release tablets

360 mg tablet: Pale orange red film-coated ovaloid tablet with imprint (debossing) 'CT' on one side, containing 360 mg mycophenolic acid formulated as a sodium salt.

Bottles of 120.....NDC 0078-0386-66

180 mg tablet: Lime green film-coated round tablet with bevelled edges and the imprint (debossing) 'C' on one side, containing 180 mg mycophenolic acid formulated as a sodium salt.

Bottles of 120.....NDC 0078-0385-66

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)[see USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight container (USP).

Handling

Tablets should not be crushed or cut.

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