Myfortic®

Immunosuppressant

DESCRIPTION AND COMPOSITION

180 mg Myfortic tablet comes as a lime green, film-coated, round tablet, with beveled edges and the imprint (debossing) "C" on one side.

360 mg Myfortic tablet comes as a pale orange-red, film-coated, ovaloid tablet with imprint (debossing) "CT" on one side.

Pharmaceutical form

Gastro-resistant tablets

Active substance

Each gastro-resistant tablet contains 180 mg or 360 mg mycophenolic acid (MPA) equivalent to 192.4 mg and 384.8 mg mycophenolate sodium.

The two dosage strengths may not be available in all countries.

Excipients

Maize starch; povidone (K-30); crospovidone; lactose; colloidal silicon dioxide; magnesium stearate.

The gastro resistant tablet coating of 180 mg Myfortic consists of hypromellose phthalate/ hydroxypropylmethylcellulose phthalate; titanum dioxide; iron oxide yellow; indigotin.

The gastro resistant tablet coating of 360 mg Myfortic consists of hypromellose phthalate/ hydroxypropylmethylcellulose phthalate; titanium dioxide; iron oxide yellow; iron oxide red.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Myfortic is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended dose is 720 mg (four 180 mg or two 360 mg Myfortic gastro-resistant tablets) twice daily (1,440 mg daily dose). In patients receiving 2 g mycophenolate mofetil (MMF), treatment can be replaced by 720 mg twice daily (1,440 mg daily dose) of Myfortic.

General target population

Treatment with Myfortic should be initiated and maintained by appropriately qualified transplant specialists.

Myfortic should be initiated in *de novo* patients within 48 hours following transplantation.

Myfortic can be taken with or without food.

Special populations

Renal impairment

No dose adjustments are needed in patients experiencing delayed post-operative renal graft function (see section Pharmacokinetics). Patients with severe chronic renal impairment (glomerular filtration rate <25 mL • min^{-1} • 1.73 m^{-2}) should be carefully monitored.

Hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease.

Pediatric patients (below 18 years)

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

Geriatric patients (65 years of age or above)

No dose adjustment is required in this patient population.

Treatment during rejection episodes

Renal transplant rejection does not affect mycophenolic acid pharmacokinetics; dosage reduction or interruption of Myfortic is not required.

Method of administration

Myfortic tablets should not be crushed in order to maintain the integrity of the enteric coating (see section CLINICAL PHARMACOLOGY and section INSTRUCTIONS FOR USE AND HANDLING).

CONTRAINDICATIONS

Myfortic should not be used in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients (see section DESCRIPTION AND COMPOSITION).

Myfortic should not be used in women of child bearing potential (WOCBP) who are not using highly effective contraception methods.

Myfortic should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Myfortic should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Myfortic should not be given to women who are breastfeeding (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

WARNINGS AND PRECAUTIONS

Patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)

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

Pregnancy, lactation, females and males of reproductive potential

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic therapy, during therapy and for six weeks following therapy discontinuation (see PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45 to 49%) and congenital malformations (estimated rate of 23 to 27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore Myfortic is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL. (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Myfortic. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)
Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy every effort to avoid pregnancy during treatment should be taken. Therefore women with childbearing potential must use at least one form reliable contraception (section CONTRAINDICATIONS) before starting Myfortic therapy, during therapy and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Educational materials
In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

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 at least 90 days following discontinuation of mycophenolate.

Myfortic contains sodium.
This medicinal product contains 13 mg of sodium per tablet of Myfortic 180 mg, equivalent to 0.65 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 26 mg of sodium per tablet of Myfortic 360 mg, equivalent to 1.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Excipients with known effect:
Myfortic contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section ADVERSE DRUG REACTIONS). 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 of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a high protection factor sunscreen.

Infections

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

Oversuppression of the immune system increases susceptibility to infection including opportunistic infections, fatal infections and sepsis (see section ADVERSE DRUG REACTIONS).

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. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives which include mycophenolate mofetil and mycophenolate sodium (see section ADVERSE DRUG REACTIONS). The reported cases generally had risk factors for PML, including

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. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, should be included in the differential diagnosis in immunosuppressed patients with deteriorating renal function (see section ADVERSE DRUG REACTIONS). Consideration should be given to reducing the total immunosuppression in patients who develop PML or PVAN. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Blood dyscrasias

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anemia - see section ADVERSE DRUG REACTIONS), which may be related to MPA itself, comedication, viral infections, or some combination of these causes. Patients taking Myfortic should have complete blood cell counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly throughout the first year. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count $<1.5 \times 10^3$ / micro L or anemia) it may be appropriate to interrupt or discontinue Myfortic.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressants (see section ADVERSE DRUG REACTIONS). The mechanism for MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. However, MPA derivatives may cause blood dyscrasias (see above). In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. 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.

Vaccinations

Patients should be advised that vaccinations may be less effective during treatment with MPA and the use of the live attenuated vaccines should be avoided (see section INTERACTIONS). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal disorders

As 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.

Combination with other agents

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte globulin, basiliximab, ciclosporin for microemulsion and corticosteroids. The efficacy and safety of the use of Myfortic with other immunosuppressants have not been studied.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The following undesirable effects cover adverse drug reactions from two controlled clinical trials. The trials evaluated the safety of Myfortic and mycophenolate mofetil in 423 de novo and in 322 maintenance renal transplant patients (randomized 1:1); the incidence of adverse events was similar between treatments in each population.

The very common (≥10%) adverse drug reactions associated with Myfortic in combination with ciclosporin for microemulsion and corticosteroids include leukopenia and diarrhoea.

Malignancies

Patient receiving immunosuppressive regimens involving combinations of drugs, including MPA, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section WARNINGS AND PRECAUTIONS). Overall rates of malignancies observed in Myfortic clinical trials are as follows: lymphoproliferative disease or lymphoma developed in 2 de novo patients (0.9%) and in 2 maintenance patients (1.3%) receiving Myfortic for up to 1 year; non-melanoma skin carcinomas occurred in 0.9% of de novo and 1.8% of maintenance patients receiving Myfortic for up to 1 year; other types of malignancy occurred in 0.5% of de novo and 0.6% of maintenance patients.

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section WARNINGS AND PRECAUTIONS). The most common opportunistic infections in de novo renal transplant patients receiving Myfortic with other immunosuppressants in controlled clinical trials of renal transplant patients followed for 1 year were CMV (cytomegalovirus), candidiasis and herpes simplex. The overall rate of CMV infections (serology, viremia or disease) observed in Myfortic clinical trials was reported in 21.6% of de novo and in 1.9% of maintenance renal transplant patients.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (Table 1) are ranked by frequency, with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 below contains adverse drug reactions possibly or probably related to Myfortic reported in the two phase III randomized, double blind, controlled, multi-center trials: 1 in de novo kidney transplant patients and 1 in maintenance kidney transplant patients, in which Myfortic was administered at a dose of 1,440 mg /day for 12 months together with ciclosporin microemulsion and corticosteroids. It is compiled according to MedDRA system organ class.

Table 1 Adverse drug reactions possibly or probably related to Myfortic reported in the two phase III pivotal trials

Infections and infestations	
Very common	Viral, bacterial and fungal infections
Common	Upper respiratory tract infections, pneumonia
Uncommon	Wound infection, sepsis*, osteomyelitis*
Neoplasms benign and malignant	
Uncommon	Skin papilloma*, basal cell carcinoma*, Kaposi's sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Blood and lymphatic system disorders	
Very common	Leukopenia
Common	Anaemia, thrombocytopenia
Uncommon	Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Metabolism and nutrition disorders	
Very common	Hypocalcaemia, hypokalaemia, hyperuricaemia
Common	Hyperkalaemia, hypomagnesaemia
Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Psychiatric disorders	
Common	Anxiety
Uncommon	Delusional perception*
Nervous system disorders	
Common	Dizziness, headache
Uncommon	Tremor, insomnia*
Eye disorders	
Uncommon	Conjunctivitis*, blurred vision *
Cardiac disorders	
Uncommon	Tachycardia, pulmonary oedema*
Vascular disorders	
Very common	Hypertension
Common	Aggravated hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Cough, dyspnoea, dyspnoea exertional
Uncommon	Interstitial lung disease including fatal pulmonary fibrosis, pulmonary congestion*, wheezing*
Gastrointestinal disorders	
Very common	Diarrhoea
Common	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting
Uncommon	Abdominal tenderness, pancreatitis, eructation, halitosis*, ileus*, oesophagitis*, peptic ulcer*, subileus*, gastrointestinal haemorrhage, dry mouth*, lip ulceration*, parotid duct obstruction*, gastro-oesophageal reflux disease*, gingival hyperplasia*, peritonitis*
Hepatobiliary disorders	

Common	Abnormal hepatic function tests
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, contusion*, acne
Musculoskeletal, connective tissue disorders	
Common	Arthralgia, asthenia, myalgia
Uncommon	Back pain*, muscle cramps
Renal and urinary disorders	
Common	Increased blood creatinine
Uncommon	Haematuria*, renal tubular necrosis*, urethral stricture
General disorders and administration site conditions	
Common	Fatigue, peripheral oedema, pyrexia
Uncommon	Influenza like illness, lower limb oedema *, pain, rigors*, weakness*

* Event reported in a single patient (out of 372) only.

Note: Renal transplant patients were treated with 1,440 mg Myfortic daily for up to one year. A similar profile was seen in the de novo and maintenance transplant population although the incidence tended to be lower in the maintenance patients.

Listing of adverse drug reactions from post-marketing experience

The following adverse drug reactions have been derived from post-marketing experience with Myfortic via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to MedDRA system organ class. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Immune system disorders: Hypersensitivity reactions (including anaphylaxis).

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

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

The following adverse reactions are attributed to MPA derivatives as a class effect:

Infections and infestations: Serious, sometimes life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported (see section WARNINGS AND PRECAUTIONS).

Blood and lymphatic system disorders: Agranulocytosis, neutropenia, pancytopenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressants (see section WARNINGS AND PRECAUTIONS).

Gastrointestinal disorders: Colitis, oesophagitis (including CMV-colitis and -oesophagitis), CMV gastritis, pancreatitis, intestinal perforation, gastrointestinal haemorrhage, gastric ulcers, duodenal ulcers, ileus.

Pregnancy, puerperium and perinatal conditions:

Cases of spontaneous abortion have been reported in patients exposed to mycophenolate mainly in the first trimester (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Congenital disorders:

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Geriatric population (65 years of age or older)

Geriatric patients may generally be at increased risk of adverse drug reactions due to immunosuppression. Geriatric patients receiving Myfortic as part of a combination immunosuppressive regimen, did not show an increased risk of adverse reactions, compared to younger individuals in the Myfortic clinical trials.

INTERACTIONS

Observed interactions resulting in a concomitant use not recommended

Azathioprine: It is recommended that Myfortic should not be co-administered with azathioprine because such co-administration has not been studied (see section WARNINGS AND PRECAUTIONS).

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see section WARNINGS AND PRECAUTIONS).

Observed interactions to be considered

Aciclovir: Higher plasma concentrations of both MPAG (mycophenolic acid glucuronide) and aciclovir may occur in the presence of renal impairment. Therefore, the potential exists for these two drugs to compete for tubular secretion, resulting in a further increase in the concentration of both MPAG and aciclovir. In this situation patients should be carefully monitored.

Gastroprotective agents

Antacids with magnesium and aluminium hydroxides

The absorption of mycophenolate sodium was decreased when administered with antacids. Co-administration of Myfortic and antacids containing magnesium and aluminium hydroxide results in a 37% decrease in MPA systemic exposure and a 25% decrease in MPA maximal concentration. Caution should be used when co-administering antacids (containing magnesium and aluminium hydroxide) with Myfortic.

Proton pump inhibitors

In healthy volunteers, co-administration of 1000 mg MMF and 40 mg pantoprazole twice daily led to a 27% decrease in MPA AUC and to a 57% decrease in MPA C_{max}. However, in the same study, no changes in the pharmacokinetics of MPA were observed following co-administration of Myfortic and pantoprazole.

Ganciclovir: MPA and MPAG pharmacokinetics are unaffected by the addition of ganciclovir. The clearance of ganciclovir is unchanged in the setting of therapeutic MPA exposure. However, in patients with renal impairment in which Myfortic and ganciclovir are coadministered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Tacrolimus: In a calcineurin cross-over study in stable renal transplant patients, steady state Myfortic pharmacokinetics were measured during both Neoral® and tacrolimus treatments. Mean MPA AUC was 19% higher and C_{max} about 20% lower. Conversely mean MPAG AUC and C_{max} were about 30% lower on tacrolimus treatment compared to Neoral® treatment.

Ciclosporin A: When studied in stable renal transplant patients, ciclosporin A pharmacokinetics were unaffected by steady state dosing of Myfortic.

Anticipated interactions to be considered

Cholestyramine and drugs that interfere with enterohepatic circulation: Due to its capacity to block the enteric circulation of drugs, cholestyramine may decrease the systemic exposure of MPA. Caution should be used when co-administering cholestyramine or drugs that interfere with enterohepatic circulation due to the potential to reduce the efficacy of Myfortic.

Oral contraceptives: Oral contraceptives undergo oxidative metabolism while Myfortic is metabolized by glucuronidation. A clinically significant effect of oral contraceptives on Myfortic pharmacokinetics is not anticipated. However, as 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 (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Women of child-bearing potential

Pregnancy whilst taking mycophenolate must be avoided. Therefore women of childbearing potential must use at least one form of reliable contraception (section CONTRAINDICATIONS) before starting Myfortic therapy, during therapy,and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Pregnancy

Myfortic is contraindicated during pregnancy unless there is no suitable alternative treatment available to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counseled regarding pregnancy prevention and planning.

Before starting Myfortic treatment, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL in order to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test performed 8-10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy:

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to Myfortic in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

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

In addition there have been isolated reports of the following malformations:

- microphthalmia;
- congenital choroid plexus cyst;
- septum pellucidum agenesis;
- olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity (see section NON-CLINICAL SAFETY DATA).

Men

Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil. MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures by small margins, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate. Male patients of reproductive potential should be made aware of and discuss the potential risks of fathering a child with a qualified health-care professional

Breast-feeding

MPA is excreted in milk in lactating rats. It is unknown whether Myfortic is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, Myfortic is contra-indicated in women who are breast-feeding (see section CONTRAINDICATIONS).

Fertility

No specific studies with Myfortic in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen up to a dose of 40 mg/kg and 20 mg/kg respectively (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

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

In 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 $<1.5 \times 10^3$ / micro L or anemia) it may be appropriate to interrupt or discontinue Myfortic (see section WARNINGS AND PRECAUTIONS and section ADVERSE DRUG REACTIONS).

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 very high plasma protein binding of MPA, 97%. By interfering with the

enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce systemic MPA exposure.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

MPA inhibits the proliferation of T- and B lymphocytes more potently than other cells because in contrast to other cell types that can utilize purine salvage pathways the lymphocyte proliferation is critically dependent on de novo synthesis. Thus, the mode of action is complementary to calcineurin inhibitors, which interfere with cytokine transcription and resting T-lymphocytes.

Pharmacokinetics (PK)

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal MPA concentration was approximately 1.5 to 2 hours. *In vitro* studies demonstrated that the enteric coated Myfortic formulation prevents the release of MPA under acidic conditions as in the stomach.

In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, the gastrointestinal absorption of MPA was 93% and absolute bioavailability was 72%. Myfortic pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2,160 mg. Compared to the fasting state, administration of 720 mg Myfortic with a high fat meal (55 g fat, 1,000 calories) had no effect on the systemic exposure of MPA (AUC) which is the most relevant PK parameter linked to efficacy. However there was a 33% decrease in the maximal concentration of MPA (C_{max}).

Distribution

The volume of distribution of MPA at steady state is 50 liters. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound, 97% and 82%, respectively. The free MPA concentration may increase under conditions of decreased protein binding sites (uremia, hepatic failure, hypoalbuminemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Biotransformation/metabolism

The half-life of MPA is 11.7 hours and the clearance is 8.6 L/hr. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biologic activity. In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, approximately 28% of the oral Myfortic dose is converted to MPAG by presystemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 15.7 hours and its clearance is 0.45 L/hr.

Elimination

Although negligible amounts of MPA are present in the urine (<1.0%), the majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6 to 8 hours after Myfortic dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

Pharmacokinetics in renal transplant patients on ciclosporin for microemulsion based immunosuppression

Table 2 below shows mean pharmacokinetic parameters for MPA following Myfortic administration. Single dose Myfortic pharmacokinetics predicts multiple dose and chronic dosing Myfortic pharmacokinetics. In the early post-transplant period, mean MPA AUC and mean MPA C_{max} was approximately one-half of that measured six months post-transplant.

Table 2 Mean (SD) pharmacokinetic parameters for MPA following oral administration of Myfortic to renal transplant patients on Ciclosporin for microemulsion based Immunosuppression

Adult single dose n = 24	Dose (oral)	T_{max} (hrs)	C_{max} (microgram/mL)	$AUC_{0-\infty}$ (microgram*hr/mL)
	720 mg	2	26.1 (12.0)	66.5 (22.6)
Adult Multiple dose x 6 days BID n=12	Dose (oral)	T_{max} (hrs)	C_{max} (microgram/mL)	AUC_0-12 (microgram*hr/mL)
	720 mg	2	37.0 (13.3)	67.9 (20.3)
Adult Multiple dose x 28 days BID n = 36	Dose (oral)	T_{max} (hrs)	C_{max} (microgram/mL)	AUC_0-12 (microgram*hr/mL)
	720 mg	2.5	31.2 (18.1)	71.2 (26.3)
Adult Chronic, multiple dosing BID (Study ERLB 301) n=48	Dose	T_{max} (hrs)	C_{max} (microgram/mL)	AUC_0-12 (microgram*hr/mL)
14 days post-transplant	720 mg	2	13.9 (8.6)	29.1 (10.4)
3 months post-transplant	720 mg	2	24.6 (13.2)	50.7 (17.3)
6 months post-transplant	720 mg	2	23.0 (10.1)	55.7 (14.6)
Pediatric single dose n=10	Dose	T_{max} (hrs)	C_{max} (microgram/mL)	$AUC_{0-\infty}$ (microgram*hr/mL)
	450 mg/m^2	2-2.5	31.9 (18.2)	76.2 (25.2)

Special populations

Geriatric population (65 years of age or above)

Based on preliminary data MPA exposure does not appear to vary to a clinically significant degree by age.

Pediatric population (below 18 years)

Safety and efficacy in children have not been established. Limited pharmacokinetics data are available on the use of Myfortic in children. In the table above mean (SD) MPA pharmacokinetics are shown for stable pediatric renal transplant patients on ciclosporin microemulsion based immunosuppression. Increased variability of MPA C_{max} and AUC were noted in these pediatric patients compared to adult renal transplant patients. Mean MPA AUC at this dose was higher than typically measured in adults receiving 720 mg Myfortic. The mean apparent MPA clearance was approximately 7.7 L/hr. A Myfortic dose of 200 to 300 mg/m^2 would be expected to result in a MPA AUC of 30 to 50 micrograms hr/mL.

Gender

There are no clinically significant gender differences in Myfortic pharmacokinetics.

Race/ethnicity

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

Renal impairment

MPA pharmacokinetic appeared to be unchanged over the range of normal to absent renal function. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria. Clearance of either MPA or MPAG was unaffected by hemodialysis. Free MPA may also significantly increase in the setting of renal failure. This may be due to decreased MPA plasma protein binding in the presence of high blood urea concentration.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

CLINICAL STUDIES

Two multi-center, randomized, double-blind pivotal trials were used for Myfortic (MPA) approval in adults. Both studies were reference therapy-controlled clinical studies using commercially marketed Cellcept (MMF) as the comparator. Both studies demonstrated comparable efficacy and safety to MMF. The first study included 423 adult de novo renal transplants (ERLB301) and demonstrated that MPA was equivalent to MMF in efficacy and had a comparable safety profile. The second study was conducted in 322 maintenance kidney transplant recipients (ERLB302) and demonstrated that renal transplant patients receiving MMF maintenance immunosuppressive therapy could be safely converted to MPA without compromising efficacy.

De novo adult renal transplant patients (study ERL B301)

The double-blind, double-dummy randomized de novo study (ERLB301) was conducted in 423 renal transplant patients (MPA=213, MMF=210), aged 18-75 years, and was designed prospectively to test therapeutic equivalence of MPA to MMF as measured by the incidence of efficacy failure (i.e., biopsy proven acute rejection (BPAR), graft loss, death or loss to follow up) within the first 6 months of treatment (primary endpoint) and by the incidence of death, graft loss or loss to follow-up at 12 months (co-primary endpoint).

Patients were administered either MPA 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 MPA and MMF groups, 39.4% and 42.9%, respectively, received antibody therapy as an induction treatment.

Based on the incidence of efficacy failure at 6 months (MPA 25.8% vs MMF 26.2%; 95% CI: [-8.7, +8.0]) therapeutic equivalence was demonstrated. At 12 months, the incidence of BPAR, graft loss or death was 26.3% and 28.1%, and incidence of BPAR alone was 22.5% and 24.3% for MPA and MMF, respectively. Among those with BPAR, the incidence of severe acute rejection was 2.1% with MPA and 9.8% with MMF (p=ns).

Table 3 Analysis of primary efficacy endpoint and its components at 6 and 12 months (study ERL B301)

	MPA 1.44 g/day (n = 213)	MMF 2 g/day (n = 210)	95% CI MPA-MMF
6 months	n (%)	n (%)	
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	55 (25.8)	55 (26.2)	(-8.7, 8.0)
Biopsy proven acute rejection episode	46 (21.6)	48 (22.9)	(-9.2, 6.7)
Graft loss or death	8 (3.8)	11 (5.2)	(-5.4, 2.5)
Graft loss	7 (3.3)	9 (4.3)	(-4.6, 2.6)
Death	1 (0.5)	2 (1.0)	
Lost to follow-up*	3 (1.4)	0	
12 months			
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	60 (28.2)	59 (28.1)	(-8.5, 8.6)
Biopsy proven acute rejection episode	48 (22.5)	51 (24.3)	(-9.8, 6.3)
Graft loss or death	10 (4.7)	14 (6.7)	(-6.4, 2.4)
Graft loss	8 (3.8)	9 (4.3)	(-4.3, 3.2)
Death	2 (0.9)	5 (2.4)	
Lost to follow-up*	5 (2.3)	0	

** Lost to follow-up indicates patients that were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death. The criteria for therapeutic equivalence were met: the 95% CI for the difference in incidence of the primary variable (BPAR, graft loss, death or lost to follow-up at Month 6) was entirely contained in the interval (-12%, 12%).*

The overall safety and hematologic profiles were similar between the two treatment groups. Drug-suspected AEs were 51.1% and 60.5% in the MPA vs MMF groups, respectively. No difference in overall incidence of infection was observed. The overall incidence of serious infections was 22.1% in the MPA group and 27.1% in the MMF group. The incidence of serious pneumonia was lower in the MPA group (0.5% vs 4.3%, p=0.01). No difference in the overall incidence of GI AEs was observed (80.8% vs 80%, p=ns, MPA vs MMF, respectively).

Maintenance adult renal transplant patients (study ERL B302)

The maintenance study was conducted in 322 renal transplant patients (MPA=159, MMF=163) aged 18 to 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 1:1 to MPA 1.44 g/day or MMF 2 g/day for 12 months. The efficacy endpoint was the incidence of efficacy failure (i.e., BPAR, graft loss, or death) at 6 and 12 months.

At 12 months, similar rates of efficacy failure (MPA 2.5%; MMF 6.1%; p=ns), biopsy-proven acute rejection (MPA 1.3%; MMF 3.1%; p=ns) and biopsy-proven chronic rejection (MPA 3.8%; MMF 4.9%; p=ns) were observed in both groups

Table 4 Secondary efficacy endpoints (study ERL B302)

	Myfortic 1.44 g/day (n = 159)	**MMF 2 g/day (n = 163)**	**(95% CI) Myfortic-MMF**
6 months	n (%)	n (%)	
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	6 (3.8)	10 (6.1)	(-7.1, 2.4)
Biopsy-proven acute rejection episode, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	9 (5.7)	11 (6.7)	(-6.4, 4.2)
Acute rejection	2 (1.3)	3 (1.8)	(-10.9, 5.5)
Biopsy-proven acute rejection	2 (1.3)	2 (1.2)	-
Biopsy-proven chronic rejection	4 (2.5)	4 (2.5)	-
Lost to follow-up*	4 (2.5)	6 (3.7)	-
Graft loss or death	0	2 (1.2)	-
12 months	n (%) n =110	n (%) n = 113	**-**
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	10 (9.1)	14 (12.4)	-
Biopsy-proven acute rejection episode, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	13 (11.8)	15 (13.3)	-
Lost to follow up*	7 (6.4)	8 (7.1)	
Graft loss or death	1 (0.9)	4 (3.5)	

** Lost to follow-up indicates patients that were lost to follow-up without prior BPRA, graft loss or death.*

The maintenance study also demonstrated an overall similar safety profile, with the exception of the incidence of serious infections (8.8 vs 16%, $p<0.05$, MPA vs MMF). The incidence of overall infections was 59% in each group. Less pneumonia was observed in the MPA group (1.9%) than the MMF group (4.9%), but it was not statistically significant. A similar incidence of overall GI AEs was observed (69.2 vs 61.8%, MPA vs MMF), although "any GI AE" was numerically higher in the MPA-treated patients up to 12 months (29.6% vs 24.5% at month 12), and the increase in GI severity tended to be lower in MPA patients.

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

The hematopoietic and lymphoid system were the primary organs affected in toxicology studies conducted with mycophenolate sodium in rats and mice. Aplastic, regenerative anemia was identified as the dose-limiting toxicity in MPA-exposed rodents. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) and a dose-dependent spleen enlargement 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 1440 mg/day Myfortic in renal transplant patients.

The non-clinical toxicity profile of mycophenolate sodium appears to be consistent with adverse events observed in MPA-exposed humans, which now provide safety data of more relevance to the patient population (see section ADVERSE DRUG REACTIONS).

Single oral doses of MPA are moderately well tolerated in rats (LD_{50} of 350 to 700 mg/kg), well tolerated in mice or monkeys (LD_{50} of more than 1,000 mg/kg), and extremely well tolerated in rabbits (LD_{50} of more than 6,000 mg/kg).

Reproductive toxicity

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Carcinogenicity and mutagenicity

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorigenic. The highest dose tested resulted in approximately 0.6 to 1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1440 mg/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 26-week oral carcinogenicity assay in a $P53^{\pm}$ (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 (1440 mg/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 1440 mg 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 male rats fertility 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 MRHD of 1440 mg Myfortic per day. No effects on female fertility were seen up to a dose of 20 mg/kg/day, a dose at which maternal toxicity and embryotoxicity were already observed.

Incompatibilities

Not applicable.

STORAGE

See folding box.

Myfortic should not be used after the date marked “EXP” on the pack.

Myfortic must be kept out of the reach and sight of children.

PACK SIZE

Blister packs of 50, 100 and 120 tablets per carton.

Not all pack sizes are marketed.

Instructions for use and handling

Myfortic tablets should not be crushed in order to remain the integrity of the enteric coating (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

Mycophenolate sodium has demonstrated teratogenic effects (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL). If for any reasons the Myfortic tablet is crushed, avoid inhalation or direct contact with skin or mucous membrane of the powder.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Product Registration Holder:

Novartis Corporation (M) Sdn. Bhd.

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Malaysian Package Leaflet

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® = registered trademark

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