Myfortic

Immunosuppressant

Description and composition

Pharmaceutical form

Myfortic 180 mg enteric coated tablet: comes as a lime green, film coated round tablet, with bevelled edges and imprint (debossing) “C” on one side.

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

Active substance

Each enteric coated tablet contains 180 mg or 360 mg mycophenolic acid/MPA equivalent to 192.4 and 384.4 mycophenolate sodium.

Active moiety

Mycophenolate sodium is the sodium salt of the active moiety, mycophenolic acid.

Excipients

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

The Myfortic 180 mg enteric coated tablet containing consist of hypromellose phthalate/ hydroxypropyl-methylcellulose phthalate; titanium dioxide; iron oxide yellow; indigotin.

The Myfortic 360 mg enteric coated tablet containing consist of hypromellose phthalate/ hydroxypropyl-methylcellulose phthalate; titanium dioxide; iron oxide yellow; iron oxide red.

Indications

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

Myfortic is indicated for induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis.
This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.

Dosage and administration

Dosage

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

Paediatric patients

Safety and efficacy in paediatric patients have not been established. Limited pharmacokinetic data are available for paediatric renal transplant patients (see section Clinical Pharmacology). Its use in these patients group therefore cannot be recommended.

Geriatric patients

No dose adjustment is required in this patient population.

Renal impairment

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section Pharmacokinetic properties). Patients with severe chronic renal impairment (creatinine clearance < 10 ml/min) should be carefully followed up.

Hepatic impairment

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

Lupus nephritis patients:

Adequate dose finding studies have not been performed. The prescriber should adjust the dose based on clinical response.

Induction treatment with Myfortic is administered in combination with a corticosteroid. The recommended dose is 720 mg administered twice daily (1440 mg daily dose). A daily dose of greater than 1440 mg/day has been used for induction therapy in some studies, with the maximum dose of 2160 mg/day (see ‘Clinical Trials” section). This dose may be tapered for maintenance purposes following a complete or partial response.

Method of administration

Myfortic tablets should not be crushed in order to remain the integrity of the enteric coating (see section Clinical pharmacology and section Pharmaceutical information).

Contraindications

Myfortic is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients (see section Description and composition and in pregnant women.

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, therefore, it should be avoided in patients with rare heredity deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-nyhan and Kelley-Segmiller syndrome.

Women of Child bearing potential (WOCBP), pregnancy and breast-feeding

Use of Myfortic during pregnancy is associated with an increased risk of pregnancy loss including spontaneous abortion and congenital malformations. Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. For information on use in pregnancy and contraceptive requirements see section Women of child-bearing potential, pregnancy, breast-feeding fertility and male patients. Myfortic should not be used during breast-feeding (see section Women of child-bearing potential, pregnancy, breast-feeding, fertility and male patients).

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). For Myfortic there is additional evidence of genotoxic effect. As general advice to minimise 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.

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 the 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 dyschrasias

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anaemia - see section Adverse drug reactions), which may be related to MPA itself, concomitant medications, 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 through the first year. If blood dyscrasias occur (e.g.

neutropenia with absolute neutrophil count < 1.5 x 10^3 / micro L or anaemia) it may be appropriate to interrupt or discontinue Myfortic.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents (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 during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section interaction with other medicinal products and other forms of interaction). Influenza vaccination may be of value. Prescibers should refer to national guidelines for influenza vaccinations.

Gastrointestinal disorders

Because MPA derivatives have been associated with an increased incidence of digestive systems adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation, Myfortic should be administered with caution in patients with active serious digestive systems 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 immunosuppressive agents (e.g. azathioprine) have not been studied. These combinations are therefore not recommended.

Interactions

Observed interactions resulting in a concomitant use not recommended

***Azathioprine*:** It is recommended that Myfortic should not be administered concomitantly with azathioprine because such concomitant 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 also 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 followed up.

Gastroprotective agents

Antacids with magnesium and aluminium hydroxides

The absorption of mycophenolate sodium was decreased when administered with antacids. Concomitant 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.

Pantoprazole

In healthy volunteers, concomitant administration Mycophenolate sodium enteric coated 720 mg and pantoprazole 40 mg twice daily show no changes in the pharmacokinetics of MPA (AUC and C_{max}).

***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 because of the potential to reduce the efficacy of Myfortic. No studies with antibiotic has been performed.

In addition, MPA AUC intra-subject variability was doubled when switching from Neoral® (ciclosporin) to tacrolimus. Clinicians should note this increase both in MPA AUC and variability, and adjustment to Myfortic dosing should be dictated by the clinical situation. Close clinical monitoring should be performed when a switch from one calcineurin inhibitor to another is planned.

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, given that the long term effect of Myfortic dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected (see section Women of child-bearing potential, pregnancy, breast-feeding fertility and male patients).

When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Myfortic, ciclosporin may decrease the concentration of MPA as well (by approximately 20%, extrapolated from mycophenolate mofetil data), but the exact extent of this decrease is unknown because such an interaction has not been studied. However, as efficacy studies were conducted in combination with ciclosporin, this interaction does not modify the recommended posology of Myfortic. In case of interruption or discontinuation of ciclosporin, Myfortic dosage should be re-evaluated depending on the immunosuppressive regimen.

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 (> 6 months) renal transplant patients (randomized 1:1); the incidence of adverse events was similar between treatments in each populations.
The very common (≥ 10 %) adverse drug reactions associated with the administration of Myfortic in combination with ciclosporin for microemulsion and corticosteroids include leucopenia (19.2 %) and diarrhoea (23.5%).

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 following: lymphoproliferative disease or lymphoma developed in 2 *de novo* (0.9%) patients and in 2 maintenance patients (1.3%) receiving Myfortic for up to 1 year; non-melanoma skin carcinomas occurred in 0.9% *de novo* and 1.8% maintenance patients receiving Myfortic for up to 1 year; other types of malignancy occurred in 0.5% *de novo* and 0.6% maintenance patients.

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section Special warnings and special precautions for use). 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, candidiasis and herpes simplex. The overall rate of CMV infections (serology, viraemia or disease) observed in a Myfortic clinical trial 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 reactions (Table-1) are ranked under heading of frequency, 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-centre trials: 1 in *de novo* kidney transplant patients and 1 in maintenance kidney transplant patients, in which Myfortic was administered at a dose of 1440 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	Urinary track infections, herpes zoster infection, oral candidiasis, sinusitis, upper respiratory tract infections, gastroenteritis, herpes simplex, nasopharyngitis, pneumonia
	Uncommon	Wound infection, sepsis*, osteomyelitis*
Blood and lymphatic system disorders		
	Very common	Leukopenia
	Common	Anaemia, thrombocytopenia
	Uncommon	Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Nervous system disorders		
	Common	Dizzeness, headache
	Uncommon	Tremor, insomnia*
Respiratory, thoracic and mediastinal disorders		
	Common	Cough, dyspnea, dyspnea exertional
	Uncommon	Interstitial lung disease including fatal pulmonary fibrosis, pulmonary congestion*, wheezing*
Gastrointestinal disorders		
	Very common	Diarrhea
	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*
General disorders and administration site conditions		
	Common	Fatigue, edema peripheral, pyrexia/fever
	Uncommon	Influenza like illness, oedema lower limb*, pain, rigors*, weakness*
Metabolism and nutrition disorders		
	Very common	Hypocalcemia, hypokalemia, hyperuricemia
	Common	Hyperkalemia, hypomagnesemia
	Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Skin and subcutaneous tissue disorders		
	Uncommon	Alopecia, contusion*, acne
Hepato-biliary disorders		
	Common	Hepatic function tests abnormal
Cardiac disorders		
	Uncommon	Tachycardia, pulmonary oedema*, ventricular extrasystoles*
Vascular disorders		
	Very common	Hypertension, hypotension
	Common	Aggravated hypertension
Eye disorders		
	Uncommon	Conjunctivitis*, vision blurred*
Musculoskeletal, connective tissue disorders		
	Common	Arthralgia, asthenia, myalgia

Uncommon	Back pain*, muscle cramps
Neoplasms benign and malignant	
Uncommon	Skin papilloma* Basal cell carcinoma*, Kaposi's sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Psychiatric disorders	
Common	Anxiety
Uncommon	Abnormal dreams*, delusional perception*
Renal and urinary disorders	
Common	Increased blood creatinine
Uncommon	Hematuria*, Renal tubular necrosis*, urethral stricture
Reproductive system and breast disorders	
Uncommon	Impotence

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

Note: Renal transplant patients were treated with 1440 mg Myfortic daily 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. Because 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 system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

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.

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 immunosuppressive agents (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.

Geriatric population

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression. Elderly 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.

Adverse effects from a clinical trial in lupus nephritis patients (A2420)

Myfortic was administered at a dose of 720 mg twice daily for 2 weeks and then 1080 mg twice daily (or 720 mg three times daily) for 22 weeks in an open-label trial comparing the efficacy and safety of Myfortic and a standard corticosteroid regimen (prednisolone 1 mg/kg bodyweight/day, tapered) with Myfortic and a reduced corticosteroid regimen (prednisolone 0.5 mg/kg bodyweight/day, tapered) for induction treatment of lupus nephritis. Adverse events were reported by 35/42 (83.3%) patients in the Myfortic and standard corticosteroid group and by 30/39 (76.9%) patients in the Myfortic and reduced corticosteroid group. The incidence of gastrointestinal events (standard: 18/42, 42.9%; reduced: 13/39, 33.3%), infections (standard: 25/42, 59.5%; reduced: 14/39, 35.9%), and general disorders (standard: 14/42, 33.3%; reduced: 8/39, 20.5%) were higher in the Myfortic and standard corticosteroid group compared with the Myfortic and reduced corticosteroid group.

Women of Child-bearing potential, pregnancy, breast-feeding, fertility and male patients

Women of Child-bearing potential

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained.
Women of childbearing potential must use highly effective contraception before beginning Myfortic therapy, during therapy, and for six weeks after their last dose of Myfortic (see section Interactions).

Pregnancy

Use of Myfortic during pregnancy is associated with an increased risk of congenital malformations. Although there are no adequate and well controlled studies in pregnant women conducted with Myfortic, based on data from the US National Transplant Pregnancy Registry (NTPR), use of mycophenolate mofetil in combination with other immunosuppressants during pregnancy was associated with an increased rate of 22 % (four cases in 18 liveborn with exposure) of congenital malformations, compared to the rate of 4-5% for malformations seen among transplant patients in the NTPR. Congenital malformations that have been reported with mycophenolate mofetil include outer ear and other facial abnormalities including cleft lip and palate, congenital diaphragmatic hernia, anomalies of the distal limbs heart, esophagus and kidney. Use of mycophenolate mofetil during pregnancy was also reported to be associated with increased risk of spontaneous abortion. Since MMF is converted to MPA following oral or IV administration, the above risks must be taken into account for Myfortic as well. The teratogenic potential of MPA was observed in animal studies (see section Non-clinical safety data).

Myfortic should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus. Patients should be instructed to consult their physician immediately should pregnancy occur.

Breast feeding

It is not known whether MPA is excreted in human milk.

Myfortic should not be used during breast-feeding (see section Warnings and precautions)

Because many drugs are excreted in human milk, and the potential for serious adverse reactions in breastfed newborns/infants a decision should be made whether to abstain from breast-feeding while on treatment and during 6 weeks after stopping the therapy or to abstain from using the medicinal product taking into account the importance of the drug to the mother.

Fertility

Not applicable.

Male patients

Sexually active men are recommended to use condoms during treatment, and for a total of 13 weeks after their last dose of Myfortic. In addition, female partners of the male patients are recommended to use highly effective contraception during treatment and for a total of 13 weeks after the last dose of Myfortic.

Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machines have been performed. The mechanism of action and pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

Overdosage

In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class. Accordingly an overdose of Myfortic could possibly result in oversuppression of the immune system and may increase the susceptibility to infection including opportunistic infections, fatal infections and sepsis. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count < 1.5 x 10^3/micro L or anaemia) it may be appropriate to interrupt or discontinue Myfortic (see sections Warnings and precautions and 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 enterohepatic circulation of MPA, bile acid sequestrant, such as cholestyramine, may reduce the systemic MPA exposure.

Clinical pharmacology

ATC code

Pharmacotherapeutic group: immunosuppressant (ATC code L04 A A06).

Pharmacodynamics (PD)

Mycophenolate sodium is the sodium salt of mycophenolic acid (MPA). MPA is selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (MPDH), which inhibits the de novo pathway of guanosin nucleotide synthesis without being built in to the DNA.

MPA exerts a more potent cytostatic effect on lymphocytes than on other cells because in purines, in contrast to other cell types which can utilise salvage pathways, T and B lymphocyte proliferation is critically dependent on de novo synthesis. The mode of action of MPA is thus complementary to that of the calcineurin inhibitors, which interfere with cytokine transcription and resting T-lymphocytes.

Two double-blind studies were performed comparing 720 mg Myfortic to 1000 mg Cellcept in combination with ciclosporin for microemulsion and prednisone. One study included 423 de novo patients, while the second investigated the switch from Cellcept to Myfortic in 322 stable patients on maintenance therapy.

In the pivotal study in de novo renal transplant patients treated for 12 months, the compounds were therapeutically equivalent as regards the combined primary endpoint (incidence of biopsy-proven rejection, graft loss and lost to follow-up) after 6 months (PP analysis 27.4 % vs. 27.7%, difference –0.4%(CI_{95} – 9.1 %; 8.4%). The same also applied at 12 months. Other efficacy endpoints, such as treated acute rejection reaction (23.4% v. 25.7%), rejection reaction with antibody therapy (both 4.5%) or graft loss (3.5% v. 4.0 %), were comparable with Myfortic.

Pharmacokinetics (PK)

The pharmacokinetics of Myfortic are dose-proportional and linear over the dose range of 180 to 2160 mg.

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed. The absolute bioavaibility of mycophenolic acid (MPA) is 71 %. There is a limited first-pass effect. The peak plasma concentration of MPA is attained after about 1.5-2 hours.

Compared to the fasting state, administration of Myfortic 720 mg with a high fat meal (55 g fat, 1000 calories) had no effect on the AUC of MPA. However, a 33 % decrease in the peak concentration of MPA (C_{max}) was observed. A second MPA peak is detectable approx. 6-8 hours after administration of Myfortic; this is due to enterophatic circulation.

Distribution

The steady state volume of distribution at for MPA is 50 liters. Both mycophenolic acid and mycophenolic acid glucoronide are highly protein bound (97 % and 82 %, respectively). The concentration of free MPA may increase under conditions of decreased plasma protein (uremia, liver failure, hypoalbuminemia) as well as with concomitant use of other drugs with high protein binding. This is associated with an increased risk of MPA-related adverse effects (see Special warnings and special precautions for use).

Metabolism

MPA is metabolized principally by glucoronyl transferase to form the inactive mycophenolic acid glucoronide (MPAG).

Elimination

The majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is subject to enterophatic circulation. The half life of MPA is 11.7 hours and clearance is 8.6 litres/h. The half life of MPAG is longer than that of MPA, amounting to approx. 15.7 hours. Its clearance is 0.45 litres/hour.

Pharmacokinetics in Renal Transplant Patients on ciclosporin for microemulsion based immunosuppression

Shown in the following table-2 are mean pharmacokinetic parameters for MPA following the administration of Myfortic. 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 Chronic, multiple dosing BID (Study ERLB 301) n=48	Dose	T_{max}* (hr)	C_{max} (µg/mL)	AUC 0-12 (µg x 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)
Adult Chronic, multiple dosing BID 18 months post-transplant (Study ERLB 302) n=18	Dose	T_{max}* (hr)	C_{max} (µg/mL)	AUC_{0-12} (µg x hr/mL)
	720 mg	1.5	18.9 (7.9)	57.4 (15.0)
Paediatric single dose (Study ERL 0106) n=16	Dose	T_{max}* (hrs)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg x hr/mL)
	450 mg/m^2	2.5	31.9 (18.2)	74.5 (28.3)

***median values**

Special population

Renal impairment

The plasma level of MPA was comparable over the range of normal to absent renal function (glomerular filtration rate < 5 ml/min). MPAG exposure increased with decreased renal function; in conditions of anuria, it was approx. eight times higher than normal. Clearance of both MPA and MPAG was unaffected by haemodyalisis.

Free MPA may increase significantly in the presence of renal failure. This is probably due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

Hepatic impairment

In volunteers with alcoholic cirhosis, hepatic MPAG glucoronidation processes were relatively unaffected by hepatic and by hepatic parenchymal disease. However, in patients with hepatic disease with predominantly biliary damaged, such as primary biliary cirrhosis, an effect on the enterohepatic circulation cannot be ruled out.

Children and adolescents

Data on the use of Myfortic in children and adolescents is extremely limited.

Gender

There are no clinically significant gender differences in the pharmacokinetics of Myfortic.

Elderly

Pharmacokinetics in the elderly have not been specifically studied. Increasing age does not appear to be associated with a clinically significant change in the bioavaibility of MPA.

Ethnic groups/races

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

Clinical studies

Two multi-centre randomised, 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 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 18–75 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.

Lupus nephritis

One exploratory randomised open-label 6-month study (A2420; Zeher et al., 2011) has been conducted comparing the efficacy and safety of Myfortic and a standard corticosteroid regimen (prednisolone 1 mg/kg bodyweight/day, tapered) with Myfortic and a reduced corticosteroid regimen (prednisolone 0.5 mg/kg bodyweight/day, tapered) for induction treatment of lupus nephritis. Male and female patients aged ≥ 18 years were eligible to enter the study if they met the following criteria: diagnosed with SLE, defined as meeting at least four classification criteria of the American College of Rheumatology; presence of proliferative lupus nephritis flare class III or IV (ISN/RPS classification of lupus nephritis) documented by a renal biopsy performed within 24 months preceding the study entry; proteinuria defined as >0.5 gram urine protein per gram urine creatinine at screening and baseline and clinical activity defined by serum creatinine >1.0 mg/dL (88.4 µmol/L), microscopic hematuria (>5 red cells per high power field) or presence of cellular casts were the other key inclusion criteria. The key exclusion criteria were patients with calculated creatinine clearance <30 mL/min (using the Cockcroft-Gault formula); patients having received i.v. CS bolus, oral or i.v. cyclophosphamide or MMF during the last 3 months; use of any antibodies during the last 6 months. Myfortic was administered at a dose of 720 mg twice daily for 2 weeks and then 1080 mg twice daily (or 720 mg three times daily) for 22 weeks. A total of 81 patients

with biopsy proven lupus nephritis WHO class III, IV, or V and clinical activity were treated in this study.

The primary efficacy variable was the complete remission rate at 24 weeks defined as the proportion of patients with urine protein/urine creatinine ratio < 0.5 gram urine protein per gram urine creatinine, urine sediment normalized (no cellular casts, < 5 red cells per high power field), and serum creatinine is within 10% of normal value. Secondary efficacy variables included the proportion patients in partial remission after 24 weeks of treatment, with partial response defined as a reduction in urine protein:creatinine ratio of ≥50% compared with base line, and serum creatinine within 10% of baseline value; proportion of patients with mild SLE flare after 12 and 24 weeks of treatment; disease activity index measured with BILAG score and SLEDAI index; renal function assessed by serum creatinine, creatinine clearance, glomerular filtration rate (GFR) and urine protein:creatinine ratio.

The demographic and other baseline characteristics were balanced between the two dose groups. Most patients had a histological diagnosis of Class IV lupus nephritis. At 6 months, 8/42 (19.0%) of Myfortic and standard corticosteroid-treated patients and 8/39 (20.5%) of Myfortic and reduced corticosteroid-treated patients achieved complete remission. Partial response occurred in 20/42 (47.6%) of patients in the standard dose group and 14/39 (35.9%) of patients in the low dose group. Patients in whom treatment failed included those without complete or partial remission at 6 months or who prematurely discontinued treatment during the first 24 weeks for any reason, yielding failure rates of 21/42 (50%) in the standard dose group and 23/39 (59.0%) in the low dose group. At 6 months, the mean change from baseline for urine protein to creatinine ratio decreased by 1.1 in the standard dose group and by 0.8 in the low dose group. Only one patient in the standard-dose group reported a moderate to mild SLE flare at 24 weeks. The mean BILAG and SLEDI scores decreased from Week 4 to Week 24 in both treatment groups.

Published studies:

Studies comparing the use of mycophenolate (sodium or mofetil) with intravenous cyclophosphamide (IVC) and azathioprine (AZA) in patients with proliferative lupus nephritis have been reported in the literature. Results from the two pivotal published studies with MMF in induction and maintenance therapy are given below:

The ALMs study (Appel et al., 2009) compared MMF and IVC as induction treatment for active lupus nephritis in a 24 week open-label parallel group multicentre study. 370 patients with Class III to V lupus nephritis were randomly assigned to a target dose of 3g/day MMF or 0.5 to 1.0 g/m^2 IVC. Both groups received prednisone, tapered from a maximum starting dose of 60mg/day. The primary endpoint was a pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. Secondary endpoints included complete renal remission, systemic disease activity and damage, and safety. No significant difference in response rate between the two groups was detected. The primary efficacy endpoint was achieved in 104 (56.2%) patients receiving MMF, compared with 98 (53.0%) patients receiving IVC. No significant differences were detected between the MMF and IVC groups with regard to the rates of adverse events, serious adverse events or infections.

Dooley et al., 2011 conducted a 36 month randomized, double-blind, double dummy study comparing MMF (2g per day) plus placebo and AZA (2mg per kg per day) plus placebo for the maintenance of remission in 227 patients who met the response criteria during the ALMS 6-month induction trial with either MMF or IVC. 116 patients were randomly assigned to MMF and 111 to AZA. The primary endpoint was the time to treatment failure measured as the time until the first event defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. Secondary assessments included the time to the individual components of treatment failure and adverse events. MMF was superior to AZA with respect to the primary end point, time to treatment failure (hazard ratio, 0.44; 95% confidence interval, 0.25 to 0.77; P = 0.003), and with respect to time to renal flare and time to rescue therapy (hazard ratio, <1.00; P<0.05). Observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA. Adverse events, most commonly minor

infections and gastrointestinal disorders, occurred in more than 95% of the patients in both groups (P = 0.68). Serious adverse events occurred in 33.3% of patients in the AZA group and in 23.5% of those in the MMF group (P = 0.11), and the rate of withdrawal due to adverse events was higher with AZA than with MMF (39.6% vs. 25.2%, P = 0.02).

Doses used in clinical studies

The doses of mycophenolate sodium (or the equivalent doses when administered as mycophenolate mofetil) used in the published clinical studies were varied. Doses used for induction: In the pivotal 24-week ALMS study (Appel et al., 2009) the target dose of MMF was 3g per day (equivalent of 2.16g mycophenolate sodium or 720mg three times daily). The median dosage of MMF was calculated as 2.6g/day. In another 24-week published study (Ginzler et al.,2005), patients were treated with escalating doses of MMF up to 3g per day (equivalent of 2.16g mycophenolate sodium or 720mg three times daily). In this study the mean maximum tolerated dose of MMF was 2.68g per day (equivalent to 1.93g mycophenolate sodium or nearly 720mg three times daily). Doses used for maintenance: In the pivotal long term maintenance study (Dooley et al., 2011), the target dose of MMF was 2g/day (equivalent to mycophenolate sodium 720mg twice daily); 80% of patients received a daily dose of 1.6mg or more.

Non-clinical safety data

Carcinogenesis, Mutagenesis, Impairment of fertility

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorogenic. 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 1.44 g/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 tumorogenic. Since experience with this model is limited, the results cannot be definitely evaluated at present.

The genotoxic potential of mycophenolate sodium was determined in five assays. MPA was mutagenic in the mouse lymphoma/thymidine kinase assay, the micronucleous test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mychophenolate 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 assay 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/day Myfortic.

It is probable that the mutagenic activity observed was due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.

Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day and no effect on female fertility at doses up to 20 mg/kg. These doses are five to nine times higher than the recommended clinical dose.

Animal toxicity and pharmacology

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

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

In a teratology study performed with mycophenolate sodium in rats at a dose of 1 mg/kg, malformations in the offspring such as anopthalmia, exencephaly and umbilical hernia were observed. The systemic exposure at this dose represents 0.05 times the clinical exposure at a daily dose of 1.44 g Myfortic (see Women of child-bearing potential, pregnancy, breastfeeding,fertility and male patients). In a pre- and postnatal development study in rat, mycophenolic acid (as sodium salt) caused developmental delays (abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg.

Pharmaceutical information

Incompatibilities

Not applicable.

Storage

Do not store above 30°C. Myfortic 180 mg and Myfortic 360 mg enteric coated tablet should be protected from moisture. Store in the original package and container.

Shelf-life

The expiry date is indicated on the packaging.

Instructions for use and handling and precaution

Myfortic tablets should not be crushed in order to remain the integrity of the enteric coating (see section Dosage and administration and Clinical Pharmacology).
Mycophenolate sodium has demonstrated teratogenic effects in rats and rabbits (see section Women of child-bearing potential, pregnancy, breastfeeding, fertility and male patients). Avoid inhalation or direct contact with skin or mucous membrane of the powder, in case of crushing Myfortic tablets is necessary.

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

Note: Myfortic should be kept out of the reach and sight of children.

HARUS DENGAN RESEP DOKTER

PACKAGE QUANTITIES AND REGISTRATION NUMBER

Myfortic 180 mg enteric coated tablet:
Box, 5 Blister @ 10 tablet Reg. No.

Myfortic 360 mg enteric coated tablet:
Box, 5 Blister @ 10 tablet Reg. No.

Manufactured by Novartis Pharma Produktions GmbH, Wehr, Germany for Novartis Pharma AG, Basel, Switzerland.

Packed by Lek d.d., PE PROIZVODNJA LENDAVA, Slovenia.

Imported by PT Novartis Indonesia, Jakarta, Indonesia

Leaflet based on CDS 30-Oct-13, packaging site transfer to Lek Lendava

MYFORTIC®

(mycophenolic acid as mycophenolate sodium)

Tablet salut enteric 180 mg and 360 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM : 02/03/2021

ID : EREG100005VR12000200
EREG100005VR12000201

Mohon brosur dibaca dengan seksama sebelum Anda menggunakan obat ini

Mohon agar brosur ini disimpan. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Jika Anda ingin bertanya lebih lanjut, mohon hubungi dokter atau apoteker Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Jika Anda mengalami efek samping yang berat, atau jika Anda mengalami efek samping yang tidak tertera pada brosur ini, mohon informasikan kepada dokter ataupun apoteker Anda.

Daftar Isi

1 Apakah Myfortic dan apa kegunaannya

Apakah Myfortic

Tablet salut enterik Myfortic termasuk dalam golongan obat yang dikenal sebagai imunosupresan. Imunosupresan menurunkan respon tubuh Anda terhadap benda asing termasuk organ transplan.

Apakah kegunaan Myfortic

Myfortic digunakan pada orang yang menjalani transplantasi ginjal untuk mencegah penolakan transplantasi ginjal baru oleh tubuh. Myfortic digunakan bersama obat lain yang mengandung siklosporin dan kortikosteroid.

Myfortic juga dapat digunakan untuk pengobatan lupus nefritis (kelas WHO III, IV, atau V).

Anda dapat bertanya kepada dokter jika Anda memiliki pertanyaan bagaimana cara kerja Myfortic atau mengapa obat ini diresepkan untuk Anda.

2 Sebelum Anda mengkonsumsi Myfortic

Myfortic hanya akan diresepkan kepada Anda oleh dokter yang telah memiliki pengalaman dengan obat-obatan immunosupresan/transplantasi. Ikuti instruksi dokter Anda secara seksama. Informasi ini dapat berbeda dari informasi umum yang terdapat pada brosur.

Tidak diperbolehkan mengkonsumsi Myfortic

- **Jika Anda memiliki alergi** (hipersensitif) terhadap *mycophenolic acid, mycophenolate sodium* atau *mycophenolate mofetil* atau terhadap zat tambahan lain yang terkandung dalam obat Myfortic yang terdapat pada bagian akhir brosur ini.
- **Jika Anda berpikir** bahwa Anda kemungkinan mengalami alergi, mohon agar meminta saran kepada dokter Anda.

Jika Anda mengalami hal-hal di atas, **mohon untuk tidak mengkonsumsi Myfortic dan infokan kepada dokter**.

Jika Anda berpikir Anda mengalami alergi, mohon agar Anda meminta saran kepada dokter Anda.

Perhatian khusus dalam mengkonsumsi Myfortic

- Myfortic menurunkan mekanisme pertahanan tubuh Anda. Hal ini dapat meningkatkan risiko terjadinya kanker kulit. Anda sebaiknya membatasi paparan sinar matahari dan sinar UV dengan menggunakan pakaian pelindung yang cocok dan sesering mungkin menggunakan tabir surya dengan faktor proteksi yang tinggi.
- Jika Anda sebelumnya pernah mengidap hepatitis B atau C Myfortic dapat meningkatkan resiko munculnya kembali penyakit ini. Dokter Anda dapat melakukan analisis darah dan memeriksa gejala-gejala penyakit tersebut. Jika Anda mengalami gejala-gejala ini (kulit dan mata berwarna kuning, mual, hilang nafsu makan, urin berwarna gelap) sebaiknya hubungi dokter Anda sesegera mungkin.
- Jika Anda mengalami gejala-gejala infeksi (seperti demam, sakit tenggorokan), timbulnya memar secara tiba-tiba dan/atau pendarahan, sebaiknya menghubungi dokter Anda sesegera mungkin.
- Mintalah saran kepada dokter Anda jika Anda telah menerima vaksin atau berencana untuk melakukan vaksinasi.
- Jika Anda sedang, atau pernah mengalami kelainan serius pada saluran pencernaan misalnya tukak lambung.
- Jika Anda memiliki kondisi yang diturunkan oleh keluarga Anda yaitu defisiensi enzim *hypoxanthine-guanine phosphoribosyl-transferase* (HGPRT) seperti sindrom *Lesch-Nyhan* atau sindrom *Kelley-Seegmiller*.
- Penggunaan Myfortic pada masa kehamilan dapat meningkatkan resiko cacat pada janin dan keguguran termasuk aborsi spontan (lihat bagian Wanita hamil). Jika Anda adalah wanita yang mungkin mengalami kehamilan: sebaiknya terapi menggunakan Myfortic tidak dimulai hingga tes kehamilan telah dilakukan dan hasilnya negatif dan Anda sebaiknya menggunakan kontrasepsi selama menjalani terapi dan untuk sekurang-kurangnya 6 minggu

setelah terapi dihentikan. Jika Anda hamil, atau Anda berpikir Anda hamil atau sedang berencana untuk hamil, mintalah saran kepada dokter Anda.

- Jika Anda masih menyusui (lihat bagian Ibu menyusui).

Jika Anda mengalami hal-hal tersebut di atas, **hubungi dokter Anda sebelum mengkonsumsi Myfortic**.

Penggunaan obat lain

Infokan dokter atau apoteker Anda jika Anda sedang atau baru saja mengkonsumsi obat-obatan lain.

Ingatlah agar Anda selalu menginfokan obat-obatan yang Anda beli tanpa resep dokter termasuk antasida (obat-obatan yang digunakan untuk menangani gangguan pencernaan dan rasa panas di dada).

Penting untuk menginfokan kepada dokter Anda jika Anda mengkonsumsi obat-obatan berikut ini:

- Obat imunosupresif seperti *Azathioprine*, *Tacrolimus*.
- *Cholestyramine* (obat yang digunakan untuk mengobati kadar kolesterol yang tinggi di dalam darah)
- *Aciclovir* (obat untuk mengobati infeksi herpes)
- Antasida yang mengandung magnesium dan aluminium
- *Ganciclovir* (obat yang digunakan untuk mengobat infeksi *cytomegalovirus* [CMV]
- Sebelum pemberian vaksin
- Kontrasepsi oral
- Obat untuk mengobati tukak lambung seperti *Pantoprazole*.

Penggunaan Myfortic dengan makanan dan minuman

Myfortic dapat dikonsumsi bersamaan atau tanpa makanan.

Pasien usia lanjut

Myfortic dapat diberikan kepada pasien usia lanjut, tidak diperlukan penyesuaian dosis.

Anak-anak dan remaja

Penggunaan Myfortic pada anak-anak dan remaja tidak dianjurkan.

Wanita yang mungkin mengalami kehamilan

Dokter Anda sebaiknya menyarankan penggunaan kontrasepsi sebelum Anda mengkonsumsi Myfortic. Anda harus menggunakan kontrasepsi sebelum dan selama terapi, dan selama 6 minggu setelah Anda berhenti mengkonsumsi Myfortic. Hubungi langsung dokter Anda jika Anda hamil ketika masih mengkonsumsi Myfortic.

Wanita hamil

Penggunaan Myfortic pada saat kehamilan dapat meningkatkan resiko cacat pada janin dan keguguran. Jika Anda hamil atau Anda berpikir Anda mungkin sedang hamil, atau merencanakan kehamilan, hubungi dokter Anda. Dokter Anda akan berdiskusi dengan Anda mengenai potensi resiko penggunaan Myfortic selama kehamilan.

Ibu menyusui

Infokan kepada dokter Anda jika Anda masih menyusui. Menyusui tidak diperbolehkan selama menjalani terapi menggunakan Myfortic dan selama 6 minggu setelah Anda berhenti mengkonsumsi Myfortic.

Pria

Jika Anda adalah pria yang aktif secara seksual, Anda sebaiknya Anda menggunakan kondom selama menjalani terapi dengan Myfortic dan selama 13 minggu setelah berhenti mengkonsumsi Myfortic. Pasangan Anda juga sebaiknya menggunakan kontrasepsi yang efektif selama menjalani terapi dan selama 13 minggu setelah Anda berhenti mengkonsumsi Myfortic. Infokan langsung kepada dokter jika pasangan Anda hamil ketika Anda masih mengkonsumsi Myfortic.

Mengemudi dan menggunakan mesin

Myfortic tidak akan mempengaruhi kemampuan Anda dalam mengemudi atau menggunakan mesin.

3 Bagaimana cara mengkonsumsi Myfortic

Mohon untuk selalu mengkonsumsi obat ini sesuai dengan petunjuk dokter Anda. Jangan mengkonsumi obat ini melebihi dosis yang direkomendasikan.

Berapa banyak Myfortic yang dikonsumsi

Dosis harian yang direkomendasikan adalah 1440 mg (8 tablet Myfortic 180 mg atau 4 tablet Myfortic 360 mg), diminum sebagai dosis terpisah masing-masing 720 mg. Artinya Anda mengkonsumsi 4 tablet Myfortic 180 mg atau 2 tablet Myfortic 360 mg pada pagi hari dan 4 tablet Myfortic 180 mg atau 2 tablet Myfortic 360 mg pada malam hari.

Dokter Anda akan menginfokan kepada Anda bagaimana Anda harus mengkonsumsi berapa tablet Myfortic.

Kapan dan bagaimana mengkonsumsi Myfortic

Tablet harus ditelan seutuhnya dengan segelas air.

Jangan membelah atau menghancurkan tablet.

Jangan mengkonsumsi tablet yang telah cacat atau terbelah.

Berapa lama Myfortic dikonsumsi

Jangan menghentikan atau mengubah dosis Myfortic tanpa berbicara dengan dokter Anda.

Jika Anda mengkonsumsi Myfortic lebih dari yang seharusnya

Jika Anda secara tidak sengaja mengkonsumsi tablet Myfortic terlalu banyak, hubungi dokter Anda sesegera mungkin. Anda mungkin akan membutuhkan penanganan medis.

Jika Anda lupa mengkonsumsi Myfortic

Jika Anda lupa mengkonsumsi Myfortic, konsumsilah sesegera mungkin Anda ingat, lalu lanjutkan mengkonsumsi seperti biasa. Anda dapat meminta saran kepada dokter Anda.

Jika Anda berhenti mengkonsumsi Myfortic

Jangan menghentikan penggunaan obat kecuali dokter yang meminta.

4 Efek samping yang mungkin terjadi

Seperti pada penggunaan semua obat, penggunaan Myfortic dapat menimbulkan efek samping, walaupun tidak semua pasien akan mengalaminya.

Beberapa masalah yang sering terjadi adalah susah buang air besar, diare, mual, infeksi, dan penurunan jumlah sel darah putih dalam darah.

Dokter Anda akan meminta Anda untuk melakukan pemeriksaan darah rutin untuk memantau ada tidaknya perubahan jumlah sel darah atau pada kadar zat di dalam darah Anda seperti gula, lemak, dan kolesterol.

Beberapa efek samping yang dapat menjadi serius

- Jika Anda mengkonsumsi Myfortic Anda mungkin akan menjadi lebih rentan terinfeksi dari biasanya. Hal ini dapat mempengaruhi berbagai system tubuh, paling umum adalah saluran kemih, saluran pernapasan dan kulit. Anda dapat mengalami gejala infeksi termasuk demam, menggigil, berkeringat, rasa lelah, mengantuk, atau merasa tidak bertenaga.
- Jika Anda mengalami perubahan penglihatan, hilangnya koordinasi, merasa kikuk/canggung, hilang ingatan, kesulitan berbicara atau kurang menangkap ucapan orang lain, dan lemah otot maka hal tersebut dapat menjadi tanda dan gejala infeksi pada otak yang disebut leukoensefalopati multifokal yang progresif.
- Pembesaran kelenjar, tumbuh baru atau perlebaran pertumbuhan kulit, atau perubahan pada tahi lalat dapat terjadi pada pasien yang mengkonsumsi obat-obatan imunosupresif. Pasien Myfortic yang mengalami kanker kulit atau kanker nodus limpa sangat kecil jumlahnya.
- Jika Anda mengalami hal-hal yang tidak biasa seperti rasa lelah, sakit kepala, nafas pendek ketika berolahraga atau saat istirahat, pusing, nyeri dada, wajah terlihat pucat, mungkin merupakan gejala anemia (kurangnya sel darah merah).

Jika Anda mengalami hal-hal tersebut di atas, **konsultasikan segera dengan dokter Anda**.

Berikut efek samping lainnya yang dapat terjadi:

Beberapa efek samping yang sangat sering terjadi

Beberapa efek samping berikut dapat terjadi pada lebih dari 1 dari 10 pasien

- Rendahnya jumlah sel darah putih
- Turunnya kadar kalsium di dalam darah, kadang dapat menyebabkan kram, (hipokalsemia)
- Lemah otot, spasme otot, ritme jantung yang tidak normal (kemungkinan merupakan gejala rendahnya kadar potassium dalam darah) (hipokalemia)
- Hasil tes darah yang tidak normal (tingginya kadar asam urat dalam darah) (hiperurisemia)
- Sakit kepala, pusing (kemungkinan merupakan gejala tingginya tekanan darah) (hipertensi)
- Pusing, kepala terasa ringan (kemungkinan merupakan gejala rendahnya tekanan darah) (hipotensi)
- Diare
- Infeksi bakteri, virus, atau jamur

Beberapa efek samping yang sering terjadi

Beberapa efek samping ini dapat terjadi pada 1 hingga 10 pada setiap 100 pasien

- Pendarahan atau memar terjadi lebih mudah daripada kondisi normal (gejala rendahnya kadar platelet)
- Spasme otot, ritme jantung yang tidak normal (kemungkinan merupakan gejala tingginya kadar potassium dalam darah) (hiperkalemia)
- Hasil tes darah yang tidak normal (rendahnya kadar magnesium dalam darah) (hipo magnesemia)
- Gangguan emosional yang berlebihan, gelisah (gejala kegelisahan)
- Pusing
- Sakit kepala
- Batuk
- Sakit kepala, pusing, kemungkinan disertai dengan mual (kemungkinan merupakan gejala dari tingginya tekanan darah) (hipertensi yang cukup berat)
- Napas pendek, napas terputus-putus (kemungkinan merupakan gejala kesulitan bernapas biasa atau berat)
- Nyeri (seperti contohnya pada bagian perut, lambung)
- Susah buang air besar
- Nyeri atau rasa tidak nyaman pada lambung yang diikuti oleh sulitnya mencerna makanan
- Perut kembung
- Mencret
- Mual
- Muntah

- Rasa lelah
- Demam
- Hasil tes hati atau ginjal yang tidak normal
- Nyeri otot (*arthralgia*)
- Lemah (*asthenia*)
- Nyeri otot (*myalgia*)
- Bengkak pada tangan, pergelangan, atau kaki(kemungkinan merupakan gejala dari pembengkakan perifer)
- Infeksi saluran kemih, herpes, kandidiasis oral, sinusitis, infeksi saluran pernafasan atas (ISPA), infeksi saluran pencernaan, nasofaringitis, pneumonia
- Kurang darah (anemia)

Beberapa efek samping yang jarang terjadi

Beberapa efek samping yang dapat terjadi pada kurang dari 1 pada 100 pasien

- Kista yang mengandung cairan limpa
- Sulit tidur, tremor
- Pembengkakkan pada paru-paru
- Napas pendek
- Sendawa
- Bau mulut yang tidak sedap
- Pergerakan usus yang tidak normal
- Inflamasi pada esofagus
- Terdapat darah atau bercak hitam pada feses
- Mulut kering, lecet atau luka pada mulut
- Sumbatan pada kelenjar ludah, rasa panas di dada, inflamasi pada gusi, inflamasi pada saluran cerna
- Gejala mirip flu, menggigil
- Pembengkakkan pada pergelangan kaki dan kaki
- Hilangnya nafsu makan
- Nyeri punggung, nyeri otot
- Rambut rontok
- Memar pada kulit
- Jerawat
- Jantung berdetak cepat
- Keluarnya cairan dari mata yang disertai gatal, memerah dan bengkak, dan gangguan pada penglihatan
- Salah mengerti perkataan orang lain

- Gangguan ginjal, penyempitan pada saluran urin yang tidak normal sehingga menyebabkan tidak bisa menahan keinginan buang air kecil, adanya darah di urin
- Batuk, kesulitan bernapas, nyeri saat bernapas (kemungkinan merupakan gejala penyakit paru-paru interstisial termasuk fibrosis pulmonari)
- Infeksi karena luka, sepsis, osteomielitis (infeksi tulang)
- Peningkatan kadar lemak dalam darah (hiperlipidemia)
- Peningkatan kadar kolesterol dalam darah (hiperkolesterolemia)
- Penurunan kadar fosfat dalam darah (hipofosfatemia)
- Diabetes
- Impotensi

Efek samping lainnya yang frekuensi kejadiannya tidak diketahui

(Frekuensi kejadian tidak dapat diestimasi dari data yang ada)

- Ruam
- Demam, sakit tenggorokan, infeksi yang sering terjadi (kemungkinan merupakan gejala kurangnya sel darah putih) (agranulositosis)

Beberapa efek samping yang dilaporkan oleh obat-obatan sejenis Myfortic

Beberapa efek samping tambahan telah dilaporkan pada kelas yang sama dengan Myfortic yaitu:

- Inflamasi usus atau saluran esofagus
- Nyeri perut, muntah, hilangnya nafsu makan, muntah (inflamasi pada pankreas)
- Perforasi usus
- Pendarahan pada perut atau usus
- Nyeri perut disertai atau tidak dengan bercak darah/hitam pada pup
- Pergerakan usus yang tidak normal
- Infeksi serius
- Penurunan jumlah sel darah putih atau seluruh sel darah

Jika Anda mengalamai hal-hal tersebut di atas, **hubungi dokter Anda**.

Jika Anda menyadari adanya efek samping yang belum disebutkan pada brosur ini, mohon infokan kepada dokter atau apoteker Anda. Namun, Anda jangan menghentikan terapi Anda kecuali Anda telah berdiskusi sebelumnya dengan dokter Anda.

5 Cara penyimpanan Myfortic

- Simpan pada suhu tidak lebih dari 30°C.
- Simpan pada dus aslinya.

- Jangan menggunakan Myfortic setelah tanggal kadaluarsa yang tercantum pada dus obat.
- Jangan menggunakan obat jika kemasannya rusak atau cacat.
- Jauhkan obat dari jangkauan dan penglihatan anak-anak.
- Jika ada produk atau sisa material yang sudah tidak digunakan maka harus dibuang sesuai dengan ketentuan lokal.

6 Informasi lebih lanjut

Apakah isi Myfortic

Tablet salut enterik 180 mg & 360 mg

- **Zat aktif** dari Myfortic adalah *mycophenolic acid* (sebagai *mycophenolate sodium*).
- **Zat tambahan** lain dari Myfortic 180 mg adalah**:** Ini tablet: pati jagung, povidon (K-30), krospovidon, laktosa, koloid silikon dioksida, magnesium stearat. Salut selaput: *hypromellose phthalate/hydroxypropylmethylcellulose phthalate*, titanium dioksida, *iron oxide yellow*, *indigotine*.
- **Zat tambahan** lain dari Myfortic 360 mg adalah**:** Inti tablet: pati jagung, povidon (K-30), krospovidon, laktosa, koloid silikon dioksida, magnesium stearat. Salut selaput: *hypromellose phthalate/hydroxypropylmethylcellulose phthalate*, titanium dioksida, *iron oxide yellow*, *iron oxide red*.

Bagaimana bentuk Myfortic dan isi kemasannya

Myfortic tersedia dalam bentuk tablet salut enterik.

Myfortic 180 mg berwarna hijau limau, tablet salut selaput dengan sisi membulat, dengan tepi miring dan tercetak “C” pada satu sisinya.

Myfortic 360 mg berwarna jingga/merah pucat, tablet salut selaput berbentuk oval, dengan tercetak “CT” pada satu sisinya.

Tiap tablet Myfortic 180 mg mengandung 180 mg zat aktif *mycophenolic acid* sebagai *mycophenolate sodium*.

Tiap tablet of Myfortic 360 mg contains 360 mg zat aktif *mycophenolic acid* sebagai *mycophenolate sodium*.

Kemasan

Myfortic 180 mg tablet salut enterik:

Dus, 5 blister @ 10 tablet No. Reg.

Myfortic 360 mg tablet salut enterik:
Dus, 5 blister @ 10 tablet No. Reg.

HARUS DENGAN RESEP DOKTER

Pemegang Nomor Ijin Edar

PT. Novartis Indonesia

Pabrik Pembuat

Novartis Pharma Produktions GmbH, Wehr, Jerman untuk Novartis Pharma AG, Basel, Swiss.

Dikemas oleh Lek d.d., PE PROIZVODNJA LENDAVA, Slovenia.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia

Apabila Anda memiliki pertanyaan mengenai obat ini, hubungi dokter atau apoteker Anda.

Brosur berdasarkan CDS 30-Oct-13, *packaging site transfer to Lek Lendava*