Tradename

MYFORTIC® 180 mg and 360 mg enteric-coated tablets.

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.

Enteric-coated tablets

Active substance

Each enteric coated tablet contains 180 mg or 360 mg mycophenolic acid/MPA equivalent to 192.4 and 384.8 mycophenolate sodium.

Excipients

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

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

The enteric coated tablet of 360 mg Myfortic consists 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 regimen and administration

Dosage regimen

The recommended dose is 720 mg (four 180 mg or two 360 mg Myfortic enteric-coated 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.

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.

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 (PK)). 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.

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)
- in pregnant women.
- in women who are breastfeeding (see Pregnancy, lactation, females and males of reproductive potential section).

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 heredity deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Pregnancy, lactation, females and males of reproductive potential

Use of Myfortic during pregnancy is associated with an increased risk of pregnancy loss, including spontaneous abortion and/or congenital malformations. Myfortic therapy should not be initiated in females of reproductive potential until a negative pregnancy test has been obtained. For information on use in pregnancy and contraceptive requirements see section Pregnancy, lactation, females and males of reproductive potential.

Myfortic should not be used during breast-feeding (see section Pregnancy, lactation, females and males of reproductive potential).

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 anaemia - 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 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 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 live attenuated vaccines should be avoided (see section Interactions). Influenza vaccination may be of value. Prescibers should refer to national guidelines for influenza vaccinations.

Gastrointestinal disorders

As MPA derivatives have been associated with an increased incidence of digestive systems adverse events, including infrequent cases of gastrointestinal tract ulceration, 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 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 populations.

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

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 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 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	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, hypomagnesemia
Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Psychiatric disorders	
Common	Anxiety
Uncommon	Abnormal dreams*, Delusional perception*
Nervous system disorders	
Common	Dizzeness, headache
Uncommon	Tremor, insomnia*
Eye disorders	
Uncommon	Conjunctivitis*, blurred vision*
Cardiac disorders	
Uncommon	Tachycardia, pulmonary oedema*, ventricular extrasystoles*
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*
Hepato-biliary 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*
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 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.

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.

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.

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.

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 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.

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 due to 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, 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).

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.

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk Summary

Use of Myfortic during pregnancy is associated with an increased risk of spontaneous abortion and 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 to 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 Animal 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.

Animal data

In a teratology study performed with mycophenolate sodium during organogenesis resulted in malformations including anopthalmia, exencephaly and umbilical hernia, at an oral dose as low as 1 mg/kg/day. The systemic exposure at this dose represents 0.05 times the clinical exposure at the MRHD (maximum recommended human dose) of 1440 mg/day Myfortic.

In a pre- and postnatal development study in rat oral admnistration of mycophenolic acid (as sodium salt) during gestation and lactation caused developmental delays (abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg, which is below MRHD based on body surface area.

Lactation

Risk Summary

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 Contraindications section).

Females and males of reproductive potential

Pregnancy testing

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained.

Contraception

Females

Females of reproductive potential must use effective contraception (methods that result in less than 1 % pregnancy rates) before beginning Myfortic therapy, during therapy, and for six weeks after their last Myfortic dose (see section Interactions).

Males patients

Male patients are recommended to use condoms during treatment, and for a total of 13 weeks after their last Myfortic dose. Accordingly, male patients of reproductive potential should be made aware of and discuss with a qualified health-care professional the potential risks of fathering a child or donating semen. In addition, female partners of the male patients are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment and for a total of 13 weeks after the last Myfortic dose.

Infertility

There is no data on the effect of Myfortic on human fertility. Mycophenolate sodium had no effect on male and female rat's fertility at oral doses up to 40 mg/kg/day and 20 mg/kg/day respectively, equivalent to 9 and 4.5 (calculated) times the clinical exposure at the MRHD of 1440 mg Myfortic per day (see section Non-clinical safety data).

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

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 x 10^3/micro L or anaemia) it may be appropriate to interrupt or discontinue Myfortic (see sections 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 sequestrant, such as cholestyramine, may reduce systemic MPA exposure.

Clinical pharmacology

Pharmacotherapeutic group, ATC code

Pharmacotherapeutic group: immunosuppressant (ATC code L04AA06).

Mechanism of action (MOA)

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 inhibits the proliferation of T- and B lymphocytes more potently than other cells because in contrast to other cell types which can utilize 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.

Pharmacodynamics (PD)

Refer to mechanism of action.

Pharmacokinetics (PK)

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal MPA concentration approximately 1.5-2 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, a 33 % decrease in the maximal concentration of MPA (C_{max}). A second MPA peak is detectable approx. 6-8 hours after administration of Myfortic; this is due to enterophatic circulation.

Distribution

The volume of distribution of MPA at steady state is 50 liters. Both mycophenolic acid and mycophenolic acid glucoronide are highly protein bound, 97 % and 82 %, respectively. The free MPA concentration may increase under conditions of decreased plasma 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 glucoronyl transferase to form the phenolic glucoronide 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 tts 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 . 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} (hrs)	C_{max} (microgram/mL)	AUC_{0-12} (microgram* 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)

Special population

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)

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

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 haemodyalisis. Free MPA may 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 cirhosis, hepatic MPA glucoronidation 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 damaged, such as primary biliary cirrhosis, may show a different effect.

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 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 18–75 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 3 g/day MMF or 0.5 to 1.0 g/m^2 IVC. Both groups received prednisone, tapered from a maximum starting dose of 60 mg/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 (2 g per day) plus placebo and AZA (2 mg 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 3 g per day (equivalent of 2.16 g mycophenolate sodium or 720 mg three times daily). The median dosage of MMF was calculated as 2.6 g/day. In another 24-week published study (Ginzler et al.,2005), patients were treated with escalating doses of MMF up to 3 g per day (equivalent of 2.16 g mycophenolate sodium or 720 mg three times daily). In this study the mean maximum tolerated dose of MMF was 2.68 g per day (equivalent to 1.93 g mycophenolate sodium or nearly 720 mg three times daily). Doses used for maintenance: In the pivotal long term maintenance study (Dooley et al., 2011), the target dose of MMF was 2 g/day (equivalent to mycophenolate sodium 720 mg twice daily); 80% of patients received a daily dose of 1.6 g or more.

Non-clinical safety data

Safety pharmacology and repeat dose toxicity

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 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 levels at the recommended daily 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 human, 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 (LD50 of 350 to 700 mg/kg), well tolerated in mice or monkeys (LD50 of more than 1,000 mg/kg), and extremely well tolerated in rabbits (LD50 of more than 6,000 mg/kg).

Reproductive toxicity

For information on reproductive toxicity, see section Pregnancy, lactation, females and males of reproductive potential.

Carcinogenesis and mutagenicity

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 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 tumorogenic. 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 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 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/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.

Fertility

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 effect on female fertility at doses up to 20 mg/kg, a dose at which maternal toxicity and embryotoxicity were already observed. These doses are five to nine times higher than the recommended clinical dose.

Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30ºC. Myfortic 180 mg and Myfortic 360 mg enteric coated tablet should be protected from moisture.

Store in the original package and container.

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

Shelf-life

The expiry date is indicated on the packaging.

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 for 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.

HARUS DENGAN RESEP DOKTER

PACKAGE QUANTITIES AND REGISTRATION NUMBER

Myfortic 180 mg enteric coated tablet:

Box, 5 blisters @ 10 enteric-coated tablets Reg. No. DKI2121001315A1

Myfortic 360 mg enteric coated tablet:

Box, 5 blisters @ 10 enteric-coated tablets Reg. No. DKI2121001315B1

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

Packed and released by Lek d.d., PE Proizvodnja Lendava, Slovenia.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leaflet based on CDS 31-May-2021

MYFORTIC®

(mycophenolic acid as mycophenolate sodium)

Tablet salut enterik 180 mg and 360 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM: 13/03/2026

ID: EREG10000512500251
EREG10000512500252

Mohon brosur dibaca dengan saksama sebelum Anda menggunakan obat ini

Simpan brosur ini. Anda mungkin akan membutuhkannya untuk dibaca kembali.

Obat ini diresepkan untuk Anda. Mohon untuk tidak menggunakan obat ini untuk penyakit lain. Mohon untuk tidak memberikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka meskipun gejala penyakit mereka sama dengan Anda.

Jika terjadi efek samping yang berat, atau jika Anda mengetahui adanya efek samping yang tidak disebutkan pada brosur ini, mohon informasikan kepada dokter, apoteker atau tenaga kesehatan Anda.

Jika Anda memiliki pertanyaan lebih lanjut terkait dengan obat ini, mohon tanyakan kepada dokter, apoteker atau tenaga kesehatan Anda.

Daftar Isi

1 Apakah MYFORTIC® dan apa kegunaannya
2 Apa yang perlu Anda ketahui sebelum dan ketika Anda mengonsumsi Myfortic
3 Bagaimana cara mengonsumsi Myfortic
4 Kemungkinan efek samping
5 Penyimpanan Myfortic
6 Isi dari kemasan dan information lain

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 apapun yang terlihat sebagai 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).

Jika Anda memiliki pertanyaan apapun terkait bagaimana cara kerja Myfortic atau mengapa obat ini diresepkan untuk Anda, tanyakan kepada dokter Anda.

2 Apa yang perlu Anda ketahui sebelum dan ketika Anda mengonsumsi Myfortic

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

Tidak diperbolehkan mengonsumsi 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 tercantum pada bagian akhir brosur ini.
- **Jika Anda berpikir** bahwa Anda kemungkinan memiliki alergi, Anda dapat meminta saran kepada dokter Anda.
- **Jika Anda sedang hamil.**
- **Jika Anda sedang menyusui** (lihat bagian Kehamilan dan menyusui).

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

Perhatian khusus dalam mengonsumsi Myfortic

- Myfortic dapat 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 menggunakan tabir surya dengan faktor proteksi yang tinggi sesering mungkin.
- Jika Anda sebelumnya pernah mengidap hepatitis B atau C Myfortic dapat meningkatkan risiko 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) hubungi dokter Anda sesegera mungkin.
- Jika Anda mengalami gejala-gejala infeksi (seperti demam, sakit tenggorokan), timbulnya memar dan/atau pendarahan yang tidak diharapkan hubungi dokter Anda sesegera mungkin.
- Mintalah saran kepada dokter Anda jika Anda baru saja 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 kekurangan enzim *hypoxanthine-guanine phosphoribosyl-transferase* (HGPRT) seperti sindrom *Lesch-Nyhan* (yang juga dikenal sebagai sindrom *Kelley-Seegmiller*).
- Penggunaan Myfortic pada masa kehamilan dapat meningkatkan risiko cacat pada janin dan/atau keguguran termasuk aborsi spontan (lihat bagian Kehamilan dan menyusui). Jika Anda tergolong wanita dengan umur yang masih 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

selama minimal 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 mengalami hal-hal tersebut di atas, **hubungi dokter Anda sebelum mengonsumsi Myfortic**.

Penggunaan obat lain

Infokan dokter atau apoteker Anda jika Anda sedang atau baru saja mengonsumsi 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 mengonsumsi 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 mengobati infeksi *cytomegalovirus* [CMV]
- Sebelum pemberian vaksin dengan jenis vaksin hidup (*live attenuated vaccines*)
- Kontrasepsi oral
- Obat untuk mengobati tukak lambung seperti *Pantoprazole*

Anak-anak dan remaja (di bawah 18 tahun)

Penggunaan Myfortic pada anak-anak dan remaja tidak dianjurkan.

Pasien usia lanjut (usia 65 tahun atau lebih)

Myfortic dapat diberikan kepada pasien usia lanjut di atas 65 tahun, tidak diperlukan penyesuaian dosis.

Penggunaan Myfortic dengan makanan dan minuman

Myfortic dapat dikonsumsi bersamaan atau tanpa makanan.

Kehamilan dan menyusui

Anda tidak boleh mengonsumsi Myfortic selama kehamilan. Penggunaan Myfortic pada saat kehamilan dapat meningkatkan risiko 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 risiko potensi penggunaan Myfortic selama kehamilan.

Jangan mengonsumsi Myfortic jika Anda sedang menyusui.

Wanita yang mungkin mengalami kehamilan dan pasien pria

Wanita

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

Pria

Bicarakan dengan dokter Anda terkait risiko potensial menjadi ayah atau mendonasikan semen. Anda sebaiknya menggunakan kondom selama menjalani terapi dengan Myfortic dan selama 13 minggu setelah berhenti mengonsumsi Myfortic. Pasangan wanita Anda juga sebaiknya menggunakan kontrasepsi yang efektif selama menjalani terapi dan selama 13 minggu setelah Anda berhenti mengonsumsi Myfortic. Infokan langsung kepada dokter jika pasangan Anda hamil ketika Anda masih mengonsumsi Myfortic.

Mengemudi dan menggunakan mesin

Myfortic tidak memengaruhi kemampuan Anda dalam mengemudi atau menggunakan mesin.

3 Bagaimana cara mengonsumsi Myfortic

Ikuti petunjuk dokter Anda dalam mengonsumsi obat ini secara saksama. 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 2 dosis terpisah masing-masing 720 mg. Artinya Anda mengonsumsi 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.

Dosis 720 mg pertama akan diberikan dalam waktu 48 jam setelah transplantasi.

Dokter Anda akan menginfokan kepada Anda berapa tablet Myfortic yang harus Anda konsumsi.

Kapan dan bagaimana cara mengonsumsi Myfortic

Tablet harus ditelan seutuhnya dengan segelas air.

Jangan membelah atau menghancurkan tablet.

Jangan mengonsumsi tablet yang telah cacat atau terbelah.

Berapa lama Myfortic dikonsumsi

Terapi akan dilanjutkan selama Anda membutuhkan imunosupresan untuk mencegah penolakan transplantasi ginjal.

Jika Anda mengonsumsi Myfortic lebih dari yang seharusnya

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

Jika Anda lupa mengonsumsi Myfortic

Jika Anda lupa mengonsumsi Myfortic, konsumsilah sesegera mungkin ketika Anda ingat, lalu lanjutkan mengonsumsi mengikuti jadwal seperti biasa. Anda dapat meminta saran kepada dokter Anda.

Jika Anda berhenti mengonsumsi Myfortic

Menghentikan terapi Myfortic dapat meningkatkan risiko penolakan terhadap ginjal yang ditransplantasikan ke tubuh Anda. Jangan menghentikan penggunaan obat kecuali dokter yang meminta.

4 Kemungkinan efek samping

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 memiliki gejala infeksi termasuk demam, menggigil, berkeringat, rasa lelah, mengantuk, atau merasa tidak bertenaga. Jika Anda mengonsumsi Myfortic Anda mungkin akan menjadi lebih rentan terhadap infeksi dari biasanya. Hal ini dapat mempengaruhi berbagai sistem tubuh, paling umum adalah saluran kemih, saluran pernapasan dan kulit.
- Jika Anda mengalami perubahan penglihatan, hilangnya koordinasi, merasa kikuk/ceroboh, 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.
- Jika Anda mengalami pembesaran kelenjar, tumbuh kulit baru atau pelebaran pertumbuhan kulit, atau perubahan pada tahi lalat yang sudah ada. Seperti halnya yang dapat terjadi pada pasien yang mengonsumsi pengobatan imunosupresan, beberapa pasien Myfortic dengan jumlah yang sangat kecil mengalami kanker kulit atau kanker nodus limpa.

- Jika Anda mengalami hal-hal yang tidak biasa seperti rasa lelah, sakit kepala, napas pendek ketika berolahraga atau saat istirahat, pusing, nyeri dada, wajah terlihat pucat. Hal-hal tersebut merupakan gejala anemia (kurangnya sel darah merah).

Jika Anda mengalami hal-hal tersebut di atas, **hubungi dokter Anda sesegera mungkin**.

Berikut efek samping lainnya yang dapat terjadi:

Sangat umum: *dapat terjadi pada lebih dari 1 pada setiap 10 pasien*

- Rendahnya jumlah sel darah putih
- Turunnya kadar kalsium 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)
- Diare
- Infeksi bakteri, virus, atau jamur

Umum: *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) (hipomagnesemia)
- Gangguan emosional yang berlebihan, sulit tidur (gejala kegelisahan)
- Pusing
- Pusing, kepala terasa ringan (kemungkinan merupakan gejala rendahnya tekanan darah) (hipotensi)
- 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
- Menceret
- 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)
- Kurang darah (anemia)

Tidak umum: *dapat terjadi pada kurang dari 1 pada setiap 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
- Radang pada esofagus
- Terdapat darah atau bercak hitam pada feses
- Mulut kering, lecet atau luka pada mulut
- Sumbatan pada kelenjar ludah, rasa panas di dada, radang pada gusi, radang 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 (takikardia)
- Detak jantung yang tidak beraturan (*ventricular extrasystoles*)
- 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
- Mimpi buruk

Tidak diketahui: *frekuensi kejadian tidak dapat diestimasi dari data yang ada*

- Ruam
- Demam, nyeri sendi, pembengkakkan sendi (sindrom peradangan akut yang diasosiasikan dengan inhibitor sintesis purin *de novo*)

Efek samping lainnya yang dilaporkan oleh obat-obatan sejenis Myfortic

Efek samping tambahan telah dilaporkan pada obat untuk kelas yang sama dengan Myfortic yaitu:

- Radang usus atau saluran esofagus
- Nyeri perut, muntah, hilangnya nafsu makan, mual (radang pada pankreas)
- Perforasi usus
- Pendarahan pada perut atau usus
- Nyeri perut, disertai atau tidak, bercak darah/hitam pada feses
- Pergerakan usus yang tidak normal
- Infeksi serius
- Penurunan jumlah sel darah putih atau seluruh sel darah
- Demam, sakit tenggorokan, infeksi yang sering terjadi (kemungkinan merupakan gejala kurangnya sel darah putih (*agranulocytosis*)

Jika Anda mengalami 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, jangan hentikan terapi Anda kecuali Anda telah berdiskusi sebelumnya dengan dokter Anda.

5 Penyimpanan Myfortic

- Jauhkan obat dari jangkauan dan penglihatan anak-anak.
- Jangan menggunakan Myfortic setelah tanggal kedaluwarsa yang tercantum pada dus obat.
- Simpan pada dus aslinya.
- Simpan pada suhu tidak lebih dari 30°C.
- Jangan menggunakan obat jika kemasannya rusak atau cacat.
- Jika ada produk atau sisa material yang sudah tidak digunakan maka harus dibuang sesuai dengan ketentuan lokal.

6 Isi dari kemasan dan informasi lain

Apa kandungan dari 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**:** Inti tablet: pati jagung, *povidone* (K-30), *crospovidone*, laktosa, *colloidal silicon dioxide*, *magnesium stearate*. Penyalut tablet: *hypromellose phthalate/hydroxypropylmethylcellulose phthalate*, titanium dioksida, *iron oxide yellow*, *indigotine*.
- **Zat tambahan lain** dari Myfortic 360 mg adalah**:** Inti tablet: pati jagung, *povidone* (K-30), *crospovidone*, laktosa, *colloidal silicon dioxide*, *magnesium stearate*. Penyalut tablet: *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 mengandung 360 mg zat aktif *mycophenolic acid* sebagai *mycophenolate sodium*.

Kemasan

Myfortic 180 mg tablet salut enterik:

Dus, 5 blister @ 10 tablet salut enterik No. Reg. DKI2121001315A1

Myfortic 360 mg tablet salut enterik:
Dus, 5 blister @ 10 tablet salut enterik No. Reg. DKI2121001315B1

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.

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Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

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

Informasi produk untuk pasien berdasarkan CDS 31-Mei-2021