NOVARTIS

MYFORTIC® 180/360 MG

Composition
Active substance
Mycophenolic acid (as mycophenolate sodium)

Excipients
Maize starch; povidone (K-30); crospovidone; lactose; colloidal silicon dioxide; magnesium stearate.
The gastro resistant tablet coating of Myfortic 180 mg consists of hypromellose phthalate/ hydroxypropylmethylcellulose phthalate; titanum dioxide; iron oxide yellow; indigotin.
The gastro resistant tablet coating of Myfortic 360 mg consists of hypromellose phthalate/ hydroxypropylmethylcellulose phthalate; titanum dioxide; iron oxide yellow; iron oxid red.
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit
Gastro-resistant film-coated tablets containing 180 mg (light green, round, imprinted "C") or 360 mg (orange, oval, imprinted "CT") mycophenolic acid, equivalent to 192.4 mg and 384.4 mg mycophenolate sodium.

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

Dosage / Administration
Usual dosage instructions
Treatment with Myfortic must be initiated and maintained by transplant specialists.
Myfortic therapy should be initiated within 48 hours following transplantation. The recommended dose is 720 mg twice daily (total daily dose: 1440 mg).
Myfortic can be taken with or without food. The film-coated tablets should not be crushed, in order to retain the integrity of the enteric coating.

Special dosage instructions
Children and adolescents
The safety and efficacy of Myfortic have not been investigated in children and adolescents. For this reason, its use in children and adolescents cannot be recommended.

Elderly patients
No dose adjustment is required in this patient population.

Renal impairment
No dose adjustments are needed in patients experiencing delayed renal graft function postoperatively. Patients with severe chronic renal impairment (creatinine clearance <10 ml/minute) should be carefully monitored.

Hepatic impairment
No dose adjustments are needed in renal transplant patients with severe hepatic parenchymal disease.

Contraindications
Hypersensitivity to mycophenolate sodium, mycophenolate mofetil, lactose, galactose or to any of the excipients.
Pregnancy and breast-feeding.

Warnings and precautions
Patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)
Myfortic is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. It should therefore not be used in patients with hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) deficiency, as is seen in the rare Lesch-Nyhan and Kelley-Seegmiller syndromes.

Women of child-bearing potential, pregnancy and breast-feeding
Use of Myfortic is associated with an increased risk of congenital malformations. Myfortic therapy must not be initiated in women of child-bearing potential until a negative pregnancy test has been obtained (see "Pregnancy / Lactation").

Malignancies
Patients being treated with immunosuppressive substances (including Myfortic), in particular over long periods and at high doses, are at increased risk of developing lymphomas or other malignancies, particularly of the skin (see "Adverse effects"). For Myfortic, there is additional evidence of a genotoxic effect (see "Preclinical data"). Generally, to reduce the risk of skin cancer, exposure to sunlight and UV light should be limited as much as possible by wearing protective clothing and using a sunscreen with a high protection factor.

Infections
Severe suppression of the immune system increases susceptibility to infection, including opportunistic infections, fatal infections and sepsis (see "Adverse effects").
Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolic acid (MPA) derivatives. These include mycophenolate mofetil (MMF, CellCept®) and mycophenolate sodium (Myfortic®), see "Adverse effects". Progressive multifocal leukoencephalopathy is an opportunistic infection of the CNS caused by the JC virus. The underlying disease, concurrent use of other immunosuppressants and the long latency period of encephalopathy make it difficult to assess the causal association, but a possible involvement of mycophenolic acid in the pathogenesis of this condition cannot be ruled out. In immunosuppressed patients with neurological symptoms, physicians should consider progressive multifocal leukoencephalopathy in the differential diagnosis.
Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infection, should be included in the differential diagnosis of immunosuppressed patients with deteriorating renal function (see "Adverse effects").

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. Influenza vaccination may be of value. Prescribers should follow national guidelines for influenza vaccination.

Gastrointestinal disorders
As MPA has been associated with adverse effects on the gastrointestinal system, including rare cases of peptic ulcer, haemorrhage and perforation, Myfortic should be administered with caution in patients with severe, active gastrointestinal disease.

Blood count changes
Patients receiving Myfortic should be monitored for neutropenia or anaemia, which may be associated with MPA therapy itself, or may result from concomitant medications, viral infection, or some combination of these potential causes.
Complete blood counts should be performed weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. If neutropenia with an absolute neutrophil count $<1.5\times10^3$/µl or anaemia occur, it may be necessary to interrupt or completely discontinue Myfortic therapy.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid in combination with other immunosuppressive agents. It is not known how mycophenolic acid induces PRCA, or what influence is exerted by other immunosuppressants and their combinations. In some cases, PRCA was reversible following dose reduction or cessation of therapy. In transplant patients, reduced immunosuppression means an increased risk of graft rejection. Changes to Myfortic therapy should therefore only be undertaken under close supervision in transplant recipients in order to minimize the risk of graft rejection.
Patients receiving Myfortic should be instructed to immediately report any sign of infection, unexplained bruising, bleeding or any other symptoms of bone marrow depression to their doctor.
Myfortic contains lactose. Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Myfortic.

Interactions
Effect of the drug on 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 Myfortic in combination with other immunosuppressive agents, such as azathioprine and tacrolimus, have not been studied. It is recommended not to administer Myfortic concomitantly with azathioprine because both drugs may cause bone marrow aplasia. For tacrolimus, see "Interactions".

Gastroprotective agents
Antacids containing magnesium and aluminium hydroxide
Concomitant administration of Myfortic and antacids containing magnesium and aluminium hydroxide resulted in a 37% decrease in the AUC of MPA and a 25% decrease in peak concentrations of MPA. Concomitant administration of antacids (containing magnesium and aluminium hydroxide) should therefore be avoided.

Proton-pump inhibitors
In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of Myfortic and pantoprazole (40 mg twice daily for the four preceding days).

Colestyramine and other drugs that affect enterohepatic circulation: Due to its capacity to block the primary absorption and enterohepatic circulation of drugs, colestyramine may decrease the bioavailability of MPA. Co-administration of colestyramine or other drugs that affect the enterohepatic circulation, e.g. antibiotics, may reduce the efficacy of Myfortic and must therefore be accompanied by close monitoring of MPA levels. No studies with antibiotics have been performed.

Tacrolimus: In a crossover study in maintenance renal transplant patients, the steady-state pharmacokinetics of MPA and MPAG (mycophenolic acid glucuronide) were measured during both ciclosporin and tacrolimus treatment. The mean AUC of MPA was 19% higher and C_{max} about 20% lower on tacrolimus treatment compared to ciclosporin treatment. The mean AUC and C_{max} of MPAG were about 30% lower on tacrolimus treatment compared to ciclosporin treatment. MPA levels should be monitored and the dose of Myfortic adjusted if necessary when switching from the combination of ciclosporin and Myfortic to tacrolimus and Myfortic (see "Warnings and precautions").

Ciclosporin A: The pharmacokinetics of ciclosporin for microemulsion are unaffected by steady-state dosing of Myfortic.

Effect of other agents on the drug
Aciclovir and other drugs subject to active tubular secretion may compete with MPAG for tubular secretion. Patients receiving such combinations should be carefully monitored.

Ganciclovir: MPA and MPAG pharmacokinetics are unaffected by concomitant administration of ganciclovir. Therapeutic MPA plasma concentrations do not have an effect on the clearance of ganciclovir. However, in patients with renal impairment in whom Myfortic and ganciclovir are co-administered, the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Oral contraceptives: As the effect of Myfortic therapy on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected.

Pregnancy / Lactation
Pregnancy
Myfortic is contraindicated during 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 live-born infants with exposure) of congenital malformations, compared to the rate of 4-5% for malformations seen among female 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, and anomalies of the distal limbs, heart, oesophagus and kidney. Use of mycophenolate mofetil during pregnancy was also reported to be associated with an increased risk of spontaneous abortion. Since MMF is converted to MPA following oral or i.v. administration, the above risks must be taken into account for Myfortic as well.
The teratogenic potential of MPA was observed in animal studies (see "Preclinical data").
For these reasons, Myfortic is contraindicated during pregnancy and should not be taken unless a reliable method of contraception is used.
As a general rule, a negative pregnancy test result must be obtained in women of child-bearing potential (by beta hCG serum or urine testing with a sensitivity of at least 50 mIU/ml) within the week preceding the start of Myfortic therapy. The doctor should only initiate Myfortic therapy once a negative pregnancy test result is available.
Effective contraception must be used before and during treatment, and for six weeks following discontinuation of Myfortic therapy, even in women with a history of infertility, unless this is due to hysterectomy or sterilization (bilateral tubal ligation). Two reliable forms of contraception must be used simultaneously, unless abstinence from sexual relations is the chosen method. Female patients should be instructed to consult their doctor immediately if they become pregnant. If a woman becomes pregnant during treatment, she and her doctor should discuss the desirability of continuing the pregnancy (see "Interactions").
Sexually active men are advised to use condoms during treatment and for a total of 13 weeks after their last dose of Myfortic. In addition, their female partners are advised to use a reliable method of contraception during treatment and for a total of 13 weeks after the last dose of Myfortic.

Lactation
It is not known whether MPA is excreted in human milk.
Myfortic should not be used during breast-feeding (see "Warnings and precautions").
Because many drugs are excreted in human milk and may give rise to serious adverse effects in breastfed newborns/infants, a decision should be made whether to abstain from breast-feeding while on treatment and during 6 months after stopping the therapy, or to abstain from using the drug, taking into account the necessity of treatment.

Effects on ability to drive and use machines
There have been no studies of the effects of this product on the ability to drive or use machines. The adverse effects reported so far indicate that effects of this kind are unlikely.

Adverse effects
Summary of the safety profile
The following adverse effects were observed in two controlled clinical trials with Myfortic versus mycophenolate mofetil (randomized 1:1) in combination with ciclosporin for microemulsion and corticosteroids in 423 *de novo* transplant patients and 322 maintenance patients (those with > 6 months since transplantation). The incidence of adverse events was similar for both treatments in each population.
The most common adverse effects are leukopenia (19.2%) and diarrhoea (23.5%).
Elderly patients are generally at increased risk of adverse effects due to immunosuppression.

Malignancies: Patients receiving immunosuppressive therapy with combinations of drugs, including MPA, are at increased risk of lymphoma and other malignancies, particularly of the skin (see "Warnings and precautions"). Lymphoproliferative disease or lymphoma were reported in 2 *de novo* transplant patients (0.9 %) and in 2 maintenance patients (1.3%). Non-melanoma skin carcinomas occurred in 0.9% of *de novo* and 1.8% of maintenance patients. Other types of malignancy were reported in 0.5% of *de novo* and 0.6% of maintenance patients.

Opportunistic infections: All transplant patients are at increased risk of opportunistic infections. This risk rises as immunosuppression increases (see "Warnings and precautions"). In *de novo* renal transplant patients treated with Myfortic in combination with other immunosuppressants in controlled studies, and followed up for one year, infections with CMV, candida and herpes simplex occurred most frequently. CMV infections (serology, viraemia or disease) were reported in 21.6% of *de novo* transplant patients and in 1.9% of maintenance patients.

Adverse effects that may be related to Myfortic (reported in phase III trial)
Adverse effects suspected to be related to MPA, and reported in ≥10% or 1 to <10% of renal transplant patients who received Myfortic in combination with ciclosporin and corticosteroids in one of the controlled clinical trials, are listed below.

Frequencies:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000).

Infections and infestations
Very common: Viral, bacterial and fungal infections (up to 22.1%), such as urinary tract infection, herpes zoster infection, oral candidiasis, sinusitis, gastroenteritis, herpes simplex infection, nasopharyngitis.
Common: Upper respiratory tract infections, pneumonia.
Uncommon: Wound infection.
Isolated cases of sepsis and osteomyelitis were reported.

Neoplasms benign and malignant
Uncommon: Lymphoproliferative disorders.
Isolated cases of skin papilloma, basal cell carcinoma, Kaposi's sarcoma and squamous cell carcinoma were reported.

Blood and lymphatic system disorders
Very common: Leukopenia (19.2%).
Common: Anaemia, thrombocytopenia.
Isolated cases of lymphocele, lymphopenia and neutropenia were reported.

Psychiatric disorders
Isolated cases of delusional perception were reported.

Metabolism and nutrition disorders
Uncommon: Loss of appetite, hyperlipidaemia, hypophosphataemia.
Isolated cases of diabetes mellitus and hypercholesterolaemia were reported.

Nervous system disorders
Common: Headache.
Uncommon: Tremor.
An isolated case of insomnia was reported.

Eye disorders
Isolated cases of conjunctivitis and blurred vision were reported.

Cardiac disorders
Uncommon: Tachycardia.
Isolated cases of pulmonary oedema and ventricular extrasystoles were reported.

Respiratory disorders
Common: Cough.
Isolated cases of pulmonary congestion and wheezing were reported.

Gastrointestinal disorders
Very common: Diarrhoea (23.5%).
Common: Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting.
Uncommon: Abdominal tenderness, pancreatitis, eructation, gastrointestinal haemorrhage.
Isolated cases of halitosis, ileus, oesophagitis, peptic ulcer, subileus, dry mouth, lip ulceration, parotid duct obstruction, gastro-oesophageal reflux disease, gingival hyperplasia and peritonitis were reported.

Hepatobiliary disorders
Common: Hepatic function tests abnormal.

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, contusion.
Rare: Rash.

Musculoskeletal disorders
Uncommon: Muscle cramps.
Isolated cases of arthritis and back pain were reported.

Renal and urinary disorders
Common: Increased blood creatinine.
Uncommon: Urethral stricture.
Isolated cases of haematuria and renal tubular necrosis were reported.

General reactions
Common: Fatigue, pyrexia.
Uncommon: Influenza-like illness, pain.
Isolated cases of lower limb oedema, rigors and weakness were reported.

The following adverse effects have been associated with a class effect of mycophenolic acid derivatives:
Colitis and oesophagitis (including CMV colitis and oesophagitis), CMV gastritis, pancreatitis, intestinal perforation, gastrointestinal haemorrhage, gastric ulcers, duodenal ulcers, ileus, severe and sometimes life-threatening infections including meningitis, infectious endocarditis, tuberculosis and atypical mycobacterial infection, polyomavirus-associated nephropathy (PVAN), especially due to BK virus infection, cases (sometimes fatal) of progressive multifocal leukoencephalopathy (PML), 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 "Warnings and precautions").

Overdose
There have been some reports of deliberate or accidental overdose with Myfortic, in which not all patients experienced the expected adverse effects. In the overdose cases in which adverse effects were reported, these fall within the known safety profile of this class of agents. Accordingly, an overdose of Myfortic may possibly result in oversuppression of the immune system, which increases susceptibility to infection, including opportunistic infections, fatal infections and sepsis. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count $<1.5\times10^3$/µl or anaemia), it may be appropriate to interrupt or discontinue Myfortic.
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, bile acid sequestrants such as colestyramine may reduce systemic MPA exposure.

Properties / Actions
ATC code: L04AA06
Mycophenolate sodium is the sodium salt of mycophenolic acid (MPA). MPA is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation to DNA.
Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells. The mechanism of action of MPA thus complements that of calcineurin inhibitors, which interfere with cytokine transcription and resting T-lymphocytes.

Clinical efficacy
Two multicentre, randomized, double-blind trials were conducted for Myfortic (MPA) approval in adults. Both studies were reference therapy-controlled, using commercially available mycophenolate mofetil (MMF) as the comparator. The first study was conducted in 423 *de novo* renal transplant patients (ERL B301). The second study was conducted in 322 maintenance renal transplant recipients (ERL B302).

De novo adult renal transplant patients (study ERL B301)
The double-blind, double-dummy randomized *de novo* study (ERL B301) was conducted in 423 renal transplant patients (MPA=213, MMF=210) aged 18-75 years. Endpoints were treatment failure, defined as biopsy-proven acute rejection (BPAR), graft loss, death or lost to follow-up after 6 months (primary endpoint) and after 12 months of treatment (co-primary endpoint). In this respect, the study showed similar results for Myfortic and MMF.
Patients were administered either MPA (1.44 g/day) or MMF (2 g/day) in combination with ciclosporin and corticosteroids for 12 months after transplantation (first dose within 48 hours post-transplant). 41% of patients received antibody induction therapy (anti-lymphocyte or anti-thymocyte antibodies or basiliximab). Antibody therapy was administered as induction treatment to patients in both groups (MPA 39.4%, MMF 42.9%).
Regarding 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. The criteria for therapeutic equivalence were met: the 95% confidence interval (CI) for the difference in incidence of the primary endpoints (BPAR, graft loss, death or lost to follow-up after 6 months) was entirely contained in the interval (-12%, 12%). At 12 months, the observed incidence of BPAR, graft loss or death was 26.3% (MPA) and 28.1% (MMF), and of BPAR alone 22.5% (MPA) and 24.3% (MMF). Among those with BPAR, the incidence of severe acute rejection was 2.1% with MPA and 9.8% with MMF (p=ns).

Table 1: Analysis of the 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 who were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death.

Overall safety was similar between the two treatment groups and clinically acceptable for the given indication.

Maintenance adult renal transplant patients (study ERL B302)
The maintenance study was conducted at least 6 months post-transplant in 322 renal transplant patients (MPA=159, MMF=163) aged 18-75 years, who were treated with 2 g/day MMF in combination with ciclosporin with or without corticosteroids for at least four weeks prior to study entry. Patients were randomized 1:1 to MPA 1.44 g/day or MMF 2 g/day for 12 months. The aim of the study was to determine the frequency and severity of gastrointestinal events and neutropenia. The endpoint was the incidence of efficacy failure (i.e. BPAR, graft loss or death) at 6 and 12 months.
The incidence of gastrointestinal events at 3 and 12 months was numerically higher on Myfortic than on MMF (26% vs. 21% and 32 % vs. 26%, respectively). During the study, only one case of neutropenia in the MMF group was detected as an adverse event. The two groups were similar in terms of efficacy.

Pharmacokinetics
Myfortic pharmacokinetics 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 bioavailability of mycophenolic acid (MPA) in maintenance renal transplant patients given concomitant treatment with ciclosporin is 71%. There is a limited first-pass effect. Time to maximum concentration of MPA is approximately 1.5 to 2 hours.
Compared to the fasting state, administration of 720 mg Myfortic with a high-fat meal (55 g fat, 1000 calories) had no effect on the AUC of MPA. However, there was a 33% decrease in the maximum concentration of MPA (C_{max}).
Approximately 6 to 8 hours after Myfortic administration, a second MPA peak can be measured; this is due to enterohepatic circulation.

Distribution
The volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide exhibit strong plasma protein binding (97% and 82%, respectively). The free MPA concentration may increase under conditions of decreased plasma protein concentration (uraemia, hepatic failure, hypoalbuminaemia), or with concomitant use of other drugs with high plasma protein binding. This is associated with an increased risk of MPA-related adverse effects (see "Warnings and precautions").

Metabolism
MPA is metabolized principally by glucuronyl transferase to form inactive mycophenolic acid glucuronide (MPAG).

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

Pharmacokinetics in special patient populations
Renal impairment: Plasma levels of MPA were comparable over the range of normal to absent renal function (glomerular filtration rate <5 ml/minute). MPAG plasma concentrations increased with decreased renal function; in conditions of anuria, they were approximately eight times higher than normal. Clearance of both MPA and MPAG was unaffected by haemodialysis.
The free MPA concentration may increase significantly in the presence of renal failure. This is probably due to decreased plasma protein binding of MPA.

Hepatic impairment: In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation was relatively unaffected by hepatic parenchymal disease.
An effect on the enterohepatic circulation cannot be ruled out in patients with predominantly cholestatic liver disease, such as primary biliary cirrhosis.

Children and adolescents: Safety and efficacy in children and adolescents have not been studied. Limited pharmacokinetic data are available on the use of Myfortic in children. The pharmacokinetics following a single dose of 450 mg/m^2 were studied in 12 children between 5 and 10 years of age and 13 children between 11 and 16 years of age. The results were comparable to those found in adults: T_{max} 2.50 hours, $t_{1/2}$ 8.5 hours.

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

Elderly patients: There has been no specific study of pharmacokinetics in elderly patients. MPA bioavailability does not appear to change to a clinically relevant degree with increasing age.

Ethnic groups/races: Following single-dose administration of 720 mg Myfortic to 18 Japanese and Caucasian healthy volunteers, the exposure (AUC_{inf}) for MPA and MPAG was 15% and 22% lower, respectively, in the Japanese volunteers compared to the Caucasians. The peak concentrations (C_{max}) of MPAG were similar in the two populations; however, C_{max} for MPA was 9.6% higher in the Japanese.

Preclinical data
Animal toxicity and pharmacology
The haematopoietic and lymphoid systems were the primary organ systems affected in toxicology studies conducted with mycophenolate sodium in rats and mice. Mild to distinct dose-dependent aplastic, regenerative anaemia was observed in rodents exposed to MPA. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) in both rats and mice, and a dose-dependent enlargement of the spleen and increase in extramedullary haematopoiesis in mice only. Rats appear to be slightly more susceptible than mice to treatment-induced anaemia. In rats, the effect was mainly seen at doses of 20 mg/kg or higher, with systemic exposure (AUC) of 216.5 and 396.3 µ.h/ml in male and female rats, respectively. This corresponds to roughly 1.9 or 3.3 times the systemic concentrations (mean AUC of 111.4 µ.h/ml) that are equivalent to the levels after administration of the recommended dose of 1.44 g/day Myfortic to renal transplant patients.
The non-clinical toxicity profile of mycophenolate sodium appears to be consistent with adverse effects observed in humans after administration of MPA, which now provide safety data of more relevance to the patient population. (see "Adverse effects").

Reproductive and developmental toxicity
Mycophenolate sodium has no effect on the 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/day. These doses are five to nine times higher than the clinical dose.
In a teratology study in rats given mycophenolate sodium at a dose of 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic (see "Pregnancy / Lactation"). In a pre- and postnatal development study in rats, 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.

Carcinogenesis, mutagenesis
The genotoxic potential of mycophenolate sodium was determined in five assays. MPA was mutagenic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay or the chromosomal aberration assay in human lymphocytes. The lowest dose showing genotoxic effects in a mouse bone marrow micronucleus 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 Myfortic per day.
It is probable that the mutagenic activity observed was due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.
In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorigenic. The highest dose tested resulted in approximately 0.6 to 1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats given mycophenolate mofetil. In a 26-week oral carcinogenicity assay in a P53± (heterozygous) transgenic mouse model, mycophenolate sodium was not tumorigenic at daily doses of up to 200 mg/kg.
As experience with this model is limited, the results cannot be definitively evaluated at present.

Other information
Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Store in the original pack. Do not store above 30°C.
Keep out of the reach of children.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box.

Information last revised
May 2012

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists