Mycophenolic acid

Core Safety Profile

4.3 Contraindications

Hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients (see section 6.1).

Myfortic is contraindicated in women who are breastfeeding (see section 4.6).

For information on use in pregnancy and lactation and contraceptive requirements, see section 4.6.

4.4 Special warnings and precautions for use

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 4.8). 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 minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

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

Patients treated with immunosuppressants, including Myfortic, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (which include mycophenolate mofetil and mycophenolate sodium) in combination with other immunosuppressants. The mechanism for MPA derivatives induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of therapy. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see Section 4.8).

Patients receiving Myfortic should be monitored for blood disorders (e.g neutropenia or anemia - see section 4.8),, which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes.
Patients taking Myfortic should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.
If blood disorders occur (e.g neutropenia with absolute neutrophil count $<1.5 \times 10^3/\mu l$ or anemia) it may be appropriate to interrupt or discontinue Myfortic.

Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section 4.5).
Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation, Myfortic should be administered with caution in patients with active serious digestive system disease.

It is recommended that Myfortic not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated.

Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Myfortic has been administered in combination with corticosteroids and ciclosporin.
There is limited experience with its concomitant use with induction therapies such as anti-T-lymphocyte globulin or basiliximab. The efficacy and safety of the use of Myfortic with other immunosuppressive agents (for example, tacrolimus) have not been studied.

Myfortic contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The concomitant administration of Myfortic and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub-therapeutic systemic MPA exposure and reduced efficacy.

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

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic therapy, during therapy and for six weeks following therapy discontinuation (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been reported between MPA and other medicinal products:

Aciclovir and ganciclovir
The potential for myelosuppression in patients receiving both Myfortic and aciclovir or ganciclovir has not been studied. Increased levels of mycophenolic acid glucuronide (MPAG) and aciclovir/ganciclovir may be expected when aciclovir/ganciclovir and Myfortic are administered concomitantly, possibly as a result of competition for the tubular secretion pathway.
The changes in MPAG pharmacokinetics are unlikely to be of clinical significance in patients with adequate renal function. In the presence of renal impairment, the potential exists for increases in plasma MPAG and aciclovir/ganciclovir concentrations; dose recommendations for aciclovir/ganciclovir should be followed and patients carefully observed.

Gastroprotective agents:
Magnesium and aluminium containing antacids
MPA AUC and C_{max} have been shown to decrease by approximately 37% and 25%, respectively, when a single dose of magnesium-aluminium containing antacids is given concomitantly with Myfortic. Magnesium aluminium-containing antacids may be used intermittently for the treatment of occasional dyspepsia. However the chronic, daily use of magnesium-aluminium containing antacids with Myfortic is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Proton pump inhibitors:
In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of Myfortic and pantoprazole given at 40 mg twice daily during the four previous days. No data are available with other proton pump inhibitors given at high doses.

Oral contraceptives
Interaction studies between MMF and oral contraceptives indicate no interaction. Given the metabolic profile of MPA, no interactions would be expected for Myfortic and oral contraceptives.

Cholestyramine and drugs that bind bile acids
Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to decrease MPA exposure and thus reduce the efficacy of Myfortic.

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

Tacrolimus
In a calcineurin cross-over study in stable renal transplant patients, steady-state Myfortic pharmacokinetics were measured during both Neoral and tacrolimus treatment. Mean MPA AUC was 19% higher (90% CI: -3, +47), whereas mean MPAG AUC was about 30% lower (90% CI: 16, 42) on tacrolimus compared to Neoral treatment. In addition, MPA AUC intra-subject variability was doubled when switching from Neoral to tacrolimus. Clinicians should note this increase both in MPA AUC and variability, and adjustments 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.

Live attenuated vaccines
Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

4.6 Pregnancy and lactation

Pregnancy
Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic therapy, during Myfortic therapy and for six weeks after discontinuing therapy. Patients should be instructed to consult their physician immediately should pregnancy occur.

The use of Myfortic is not recommended during pregnancy and should be reserved for cases where no alternative treatment is available.
There is limited data from the use of Myfortic in pregnant women. However, congenital malformations including ear malformations, i.e. abnormally formed or absent external/middle ear, have been reported in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. Cases of spontaneous abortions have been reported in patients exposed to mycophenolic acid compounds. Studies in animals have shown reproductive toxicity (see section 5.3).

Lactation
MPA is excreted in milk in lactating rats. It is unknown whether Myfortic is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, Myfortic is contra-indicated in women who are breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

The following undesirable effects cover adverse drug reactions from clinical trials:

Malignancies

Patients 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 4.4). Lymphoproliferative disease or lymphoma developed in 2 *de novo* (0.9%) patients and in 2 maintenance patients (1.3%) receiving Myfortic for up to 1 year. Non-melanoma skin carcinomas occurred in 0.9% 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 4.4). 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 cytomegalovirus (CMV), candidiasis and herpes simplex. CMV infection (serology, viraemia or disease) was reported in 21.6% of *de novo* and in 1.9% of maintenance renal transplant patients.

Elderly patients

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

Other adverse drug reactions

Table 1 below contains adverse drug reactions possibly or probably related to Myfortic reported in the controlled clinical trials in renal transplant patients, in which Myfortic was administered together with ciclosporin microemulsion and corticosteroids at a dose of 1,440 mg/day for 12 months. It is compiled according to MedDRA system organ class.

Adverse reactions are listed according to the following categories:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)

Table 1

Infections and infestations		
	Very common:	Viral, bacterial and fungal infections
	Common:	Upper respiratory tract infections,□pneumonia
	Uncommon:	Wound infection, sepsis*, osteomyelitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
	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:	Lymphopenia*, neutropenia*, lymphadenopathy*
Metabolism and nutrition disorders		
	Uncommon:	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Psychiatric disorders		
	Uncommon:	Abnormal dreams*, Delusional perception*, insomnia *
Nervous system disorders		
	Common:	Headache
	Uncommon:	Tremor
Eye disorders		
	Uncommon:	Conjunctivitis*, vision blurred*
Cardiac disorders		
	Uncommon:	Tachycardia, , ventricular extrasystoles
Vascular disorders		
	Uncommon:	Lymphocele*
Respiratory, thoracic and mediastinal disorders		
	Common:	Cough
	Uncommon:	Pulmonary congestion*, wheezing*, pulmonary oedema*
Gastrointestinal disorders		
	Very common:	Diarrhoea
	Common:	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, nausea, vomiting
	Uncommon:	Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis*, ileus*, lip ulceration*, oesophagitis*, subileus*, tongue discolouration*, dry mouth*, gastro-oesophageal reflux disease*, gingival hyperplasia*, pancreatitis, parotid duct obstruction*, peptic ulcer*, peritonitis*
Hepato-biliary disorders		
	Common:	Liver function tests abnormal
Skin and subcutaneous tissue disorders		
	Uncommon:	Alopecia
Musculoskeletal and connective tissue disorders		
	Uncommon:	Arthritis*, back pain*, muscle cramps
Renal and urinary disorders		
	Common:	Blood creatinine increased
	Uncommon:	Haematuria*, renal tubular necrosis*, urethral stricture
Reproductive system and breast disorders		
	Uncommon:	Impotence*
General disorders and administration site conditions		

	Common:	Fatigue, pyrexia
	Uncommon:	Influenza like illness, oedema lower limb*, pain, rigors*, thirst*, weakness*
Injury, poisoning and procedural complications		
	Uncommon	Contusion *

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

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

Rash has been identified as an adverse drug reaction from post marketing experience

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

Infections and infestations:
serious, life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Myfortic (see section 4.4).

Blood and lymphatic system disorders:
neutropenia, pancytopenia.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with MPA derivatives. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive Myfortic.

Gastrointestinal disorders:
colitis, CMV gastritis, intestinal perforation, gastric ulcers, duodenal ulcers.

4.9 Overdose

There have been reports of intentional or accidental overdoses with Myfortic, whereas not all patients experienced related adverse events.
In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class (mainly blood dyscrasias, sepsis…) (see sections 4.4 and 4.8).

Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the very high plasma protein binding of MPA, 97%. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.