NOVARTIS

Myfortic®

Immunosuppressant

DESCRIPTION AND COMPOSITION

PHARMACEUTICAL FORM

Gastro-resistant tablets

Active substance

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

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

Excipients

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

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

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

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

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

Pharmaceutical formulations may vary between countries.

INDICATIONS

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

Myfortic is indicated for induction and maintenance treatment of adult patients with ISN/RPS Class III, IV or V lupus nephritis.

The evidence for efficacy was based on surrogate endpoints in studies where the majority of patients with lupus nephritis were ISN/RPS (2003) Class IV (see Clinical Studies section).

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended dose is 720 mg (four 180 mg or two 360 mg Myfortic gastro-resistant tablets)

twice daily (1440 mg daily dose). Myfortic delayed-release tablets and mycophenolate mofetil tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent.

General target population

Transplant patient

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.

Lupus nephritis patients

Adequate dose finding studies have not been performed. The prescriber should adjust the dose based on clinical response. The dose may be tapered for maintenance purposes following a complete or partial response (see Clinical Studies section).

Induction treatment with Myfortic is usually initially administered in combination with corticosteroids.

Special populations

Renal impairment

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

Hepatic impairment

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

Pediatric patients (below 18 years old)

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

Geriatric patients (65 years of age or above)

No dose adjustment is required in this patient population.

Treatment during rejection episodes

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

Method of administration

Myfortic tablets should not be crushed in order to maintain the integrity of the enteric coating (see sections CLINICAL PHARMACOLOGY and PHARMACEUTICAL INFORMATION).

CONTRAINDICATIONS

Myfortic is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients, and in pregnant women. (see section DESCRIPTION AND COMPOSITION).

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 be therefore avoided in patients with a rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Pregnancy, lactation, females and males of reproductive potential

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 mycophenolate mofetil (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). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed.

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.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Myfortic in combination with other immunosuppressants. In some of these cases, switching MPA derivatives to an alternative immunosuppressant, resulted in serum IgG levels returning to normal. Patients on Myfortic who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been reports of bronchiectasis in patients who received Myfortic in combination with other immunosuppressants. In some these cases, switching MPA derivatives to another immunosuppressant, resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have been also isolated reports of interstitial lung disease (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated for any evidence of underlying interstitial lung disease.

Blood dyscrasias

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

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressants agents (see section ADVERSE DRUG REACTIONS). The mechanism for MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. However, MPA derivatives may cause blood dyscrasias (see above). In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Vaccinations

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

Gastrointestinal disorders

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

Combination with other agents

Myfortic has been administered in combination with the following agents in clinical trials:

antithymocyte globulin, basiliximab, ciclosporin for microemulsion and corticosteroids. The efficacy and safety of the use of Myfortic with other immunosuppressants have not been studied.

INTERACTIONS

Observed interactions resulting in a concomitant use not recommended

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

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

Observed interactions to be considered

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

Gastroprotective agents

Antacids with magnesium and aluminium hydroxides

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

Proton pump inhibitors

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

Ganciclovir: Concomitant use of Myfortic with ganciclovir has not been studied. In patients taking mycophenolate mofetil, 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 whom Myfortic and ganciclovir are coadministered, the potential exists for the two drugs to compete for tubular secretion resulting in increased plasma concentrations of both drugs. Therefore, in patients with renal impairment, the dose recommendations for ganciclovir should be observed and patients carefully monitored.

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 (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.

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 enterohepatic circulation of drugs, cholestyramine may decrease the systemic exposure of MPA. Caution should be used when co-administering cholestyramine or drugs that interfere with enterohepatic circulation due to the potential to reduce the efficacy of Myfortic.

Oral contraceptives: Concomitant use of Myfortic with oral contraceptives has not been studied. Oral contraceptives undergo oxidative metabolism while Myfortic is metabolized by glucuronidation. A clinically significant effect of oral contraceptives on Myfortic pharmacokinetics is not anticipated. However, as the long term effect of Myfortic dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

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 section 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 in rats, administration of mycophenolate sodium during organogenesis resulted in malformations including anophthalmia, 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 rats oral administration 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

It is not known whether MPA is transferred into human milk. There are no data on the effects of Myfortic on the breastfed child or on milk production.

As many drugs are transferred into human milk, and due to the potential for serious adverse reactions in breast-fed newborns/infants , a decision should be made whether to abstain from breast-feeding during treatment and for 6 weeks after stopping the therapy or to abstain from using the medicinal product, taking into account the importance of the drug to the mother(see section WARNINGS AND PRECAUTIONS).

Females and males of reproductive potential patients

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

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 respective, 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).

ADVERSE DRUG REACTIONS

Summary of the safety profile

The following adverse events were observed in two controlled clinical trials with Myfortic versus mycophenolate mofetil (randomized 1:1 in combination with ciclosporin and corticosteroids in 423 *de novo* and in 322 maintenance (>6 months) renal transplant patients. The following undesirable effects cover adverse drug reactions from two controlled clinical trials. The trials evaluated the safety of Myfortic and mycophenolate mofetil in 423 *de novo* and in 322 maintenance renal transplant patients (randomized 1:1); the incidence of adverse events was similar between treatments in each population.

The very common (≥10%) adverse drug reactions associated with Myfortic in combination with ciclosporin for microemulsion and corticosteroids include 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, viremia or disease) observed in Myfortic clinical trials was reported in 21.6% of *de novo* and in 1.9% of maintenance renal transplant patients.

Tabulated summary of adverse drug reactions from clinical trials

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

Table 1 below contains adverse drug reactions possibly or probably related to Myfortic reported in the two phase III randomized, double blind, controlled, multi-center trials: 1 in *de novo* kidney transplant patients and 1 in maintenance kidney transplant patients, in which Myfortic was administered at a dose of 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*
Blood and lymphatic system disorders	
Very common	Leukopenia
Common	Anemia, thrombocytopenia
Uncommon	Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Nervous system disorders	
Common	Dizziness, headache
Uncommon	Tremor, insomnia*
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*, tongue discolouration, gastrointestinal haemorrhage, dry mouth*, lip ulceration*, parotid duct obstruction*, gastro-oesophageal reflux disease*, gingival hyperplasia*, peritonitis*
General disorders and administration site conditions	
Common	Fatigue, peripheral oedema, pyrexia
Uncommon	Influenza like illness, lower limb oedema*, pain, rigors*,thirst, weakness*
Metabolism and nutrition disorders	
Very common	Hypocalcaemia, hypokalaemia, hyperuricaemia
Common	Hyperkalaemia, hypomagnesaemia
Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, contusion*, acne
Hepato-biliary disorders	
Common	Abnormal hepatic function tests
Cardiac disorders	
Uncommon	Tachycardia, pulmonary oedema*, ventricular extrasystoles
Vascular disorders	
Very common	Hypertension
Common	Aggravated hypertension, hypotension
Eye disorders	
Uncommon	Conjunctivitis*, blurred vision*
Musculoskeletal, connective tissue disorders	
Common	Arthralgia, asthenia, myalgia
Uncommon	Arthritis, back pain*, muscle cramps
Neoplasms benign and malignant	
Uncommon	Skin papilloma*, basal cell carcinoma*,Kaposi's sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Psychiatric disorders	
Common	Anxiety
Uncommon	Abnormal dreams, delusional perception*
Renal and urinary disorders	
Common	Increased blood creatinine
Uncommon	Haematuria*, renal tubular necrosis*, urethral stricture

Reproductive system and breast disorders	
Uncommon	Impotence

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

Note: Renal transplant patients were treated with 1440 mg Myfortic daily 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.

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.

Listing of adverse drug reactions from post-marketing experience

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

Immune system disorders: Hypersensitivity reactions (including anaphylaxis)

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

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

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

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

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

Immune system disorders: Hypogammaglobulinaemia has been reported in patients receiving Myfortic in combination with other immunosuppressants.

Respiratory, thoracic and mediastinal disorders: There have been isolated reports of

interstitial lung disease in patients treated with Myfortic in combination with other immunosuppressants. There have also been reports of bronchiectasis in combination with other immunosuppressants.

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.

OVERDOSAGE

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

In overdose cases in which adverse events were reported, the events fall within the known safety profile of the class. Accordingly an overdose of Myfortic could possibly result in oversuppression of the immune system and may increase the susceptibility to infection including opportunistic infections, fatal infections and sepsis. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count $<1.5 \times 10^3$ / micro L or anemia) it may be appropriate to interrupt or discontinue Myfortic (see section WARNINGS AND PRECAUTIONS and section ADVERSE DRUG REACTIONS).

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

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

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

Pharmacokinetics (PK)

Absorption

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

the release of MPA under acidic conditions as in the stomach.

In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, the gastrointestinal absorption of MPA was 93% and absolute bioavailability was 72%. Myfortic pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2160 mg. Compared to the fasting state, administration of 720 mg Myfortic with a high fat meal (55 g fat, 1,000 calories) had no effect on the systemic exposure of MPA (AUC) which is the most relevant PK parameter linked to efficacy. However there was a 33% decrease in the maximal concentration of MPA (Cmax).

Distribution

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

Biotransformation / metabolism

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

Elimination

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

Pharmacokinetics in renal transplant patients on ciclosporin for microemulsion based immunosuppression

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

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

Adult Chronic, multiple dosing 720mg BID (Study ERLB 301) n=48	**Dose**	**Tmax* (hrs)**	**Cmax (microgram/mL)**	**AUC 0-12 (microgram*hrs/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** **720mg BID** **18 months post transplant** **(Study ERLB 302)** **n = 18**	**Dose (oral)**	**Tmax*** **(hrs)**	**Cmax** **(microgram/mL)**	**AUC 0-12** **(microgram*hrs/mL)**
	720 mg	1.5	18.9 (7.9)	57.4 (15.0)
Pediatric **450mg/m^2 single dose (study 0106 ERL) n=16**	**Dose**	**Tmax *** **(hrs)**	**Cmax** **(microgram/mL)**	**AUC 0-∞** **(microgram*hrs/mL)**
	450 mg/m^2	2.5	31.9 (18.2)	74.5 (28.3)

* median values

Special populations

Geriatric population (65 years of age or above)

Pharmacokinetics in the elderly have not formally been studied. MPA exposure does not appear to vary to a clinically significant degree by age.

Pediatric population (below 18 years)

Safety and efficacy in children have not been established. Limited pharmacokinetics data are available on the use of Myfortic in children and adolescents In the table above mean (SD) MPA pharmacokinetics are shown for stable pediatric renal transplant patients (aged 5-16 years) on ciclosporin-based immuno-suppression. Mean MPA AUC at a dose of 450 mg/m^2 was similar to that measured in adults receiving 720mg Myfortic. The mean apparent MPA clearance was approximately 6.7 L/hr/m^2.

Gender

There are no clinically significant gender differences in Myfortic pharmacokinetics.

Race/ethnicity

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

Renal impairment

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

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably

depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

CLINICAL STUDIES

Renal Transplant

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

De novo adult renal transplant patients (study ERL B301)

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

Patients were administered either MPA 1.44 g/day or MMF 2 g/day within 48 hours post-transplant for 12 months in combination with cyclosporine, and corticosteroids. In the MPA and MMF groups, 39.4% and 42.9%, respectively, received antibody therapy as an induction treatment.

Based on the incidence of efficacy failure at 6 months (MPA 25.8% vs. MMF 26.2%; 95% CI: [-8.7, +8.0]) therapeutic equivalence was demonstrated. At 12 months, the incidence of BPAR, graft loss or death was 28.2% 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 53.1% 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 0.5% and 4.3%, respectively, in MPA and MMF groups. No difference in the overall incidence of GI AEs was observed (79.8% vs 77.1%, p=ns, MPA vs. MMF, respectively).

Maintenance adult renal transplant patients (study ERL B302)

The maintenance study was conducted in 322 renal transplant patients (MPA=159, MMF=163), aged 18 to 75 years, who were at least 6 months post-transplant receiving 2 g/day MMF in combination with cyclosporine, with or without corticosteroids for at least four weeks prior to entry in the study. Patients were randomized 1:1 to MPA 1.44 g/day or MMF 2 g/day for 12 months. The efficacy endpoint was the incidence of efficacy failure (i.e., BPAR, graft loss, or death) at 6 and 12 months.

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

Table 4 Secondary efficacy endpoints (study ERL B302)

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

Biopsy-proven acute rejection episode, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	13 (11.8)	15 (13.3)	-
Lost to follow up*	7 (6.4)	8 (7.1)	
Graft loss or death	1 (0.9)	4 (3.5)	

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

The maintenance study also demonstrated an overall similar safety profile, with the exception of the incidence of serious infections (8.8 vs 16%, $p<0.05$, MPA vs. MMF). The incidence of overall infections was 59% in each group. Less pneumonia was observed in the MPA group (2.5%) than the MMF group (6.1%), but it was not statistically significant. A similar incidence of overall GI AEs within 12 months of randomization was observed (60.4 vs 61.3%, MPA vs MMF); the incidence of "any GI AE" was 26.4% vs 20.9% and 29.6% vs 24.5%, respectively, at the 3-month and 12-month visit windows.

Lupus nephritis

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

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

The demographic and other baseline characteristics were balanced between the two dose groups. Most patients had a histological diagnosis of Class IV lupus nephritis. At 6 months, 8/42 (19.0%) of Myfortic and standard corticosteroid-treated patients and 8/39 (20.5%) of Myfortic and reduced corticosteroid-treated patients achieved complete remission. Partial response occurred in 20/42 (47.6%) of patients in the standard dose group and 14/39 (35.9%) of patients in the low dose group. Patients in whom treatment failed included those without complete or partial remission at 6 months or who prematurely discontinued treatment during the first 24 weeks for any reason, yielding

failure rates of 21/42 (50%) in the standard dose group and 23/39 (59.0%) in the low dose group. At 6 months, the mean change from baseline for urine protein to creatinine ratio decreased by 1.1 in the standard dose group and by 0.8 in the low dose group. Only one patient in the standard-dose group reported a moderate to mild SLE flare at 24 weeks. The mean BILAG and SLEDI scores decreased from Week 4 to Week 24 in both treatment groups.

Published studies:

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

The ALMs study (Appel et al., 2009) compared MMF and IVC as induction treatment for active lupus nephritis in a 24 week open-label parallel group multicentre study. 370 patients with Class III to V lupus nephritis were randomly assigned to a target dose of 3g/day MMF or 0.5 to 1.0 g/m2 IVC. Both groups received prednisone, tapered from a maximum starting dose of 60mg/day. The primary endpoint was a pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. Secondary endpoints included complete renal remission, systemic disease activity and damage, and safety. No significant difference in response rate between the two groups was detected. The primary efficacy endpoint was achieved in 104 (56.2%) patients receiving MMF, compared with 98 (53.0%) patients receiving IVC. No significant differences were detected between the MMF and IVC groups with regard to the rates of adverse events, serious adverse events or infections.

Dooley et al., 2011 conducted a 36 month randomized, double-blind, double dummy study comparing MMF (2g per day) plus placebo and AZA (2mg per kg per day) plus placebo for the maintenance of remission in 227 patients who met the response criteria during the ALMS 6-month induction trial with either MMF or IVC. 116 patients were randomly assigned to MMF and 111 to AZA. The primary endpoint was the time to treatment failure measured as the time until the first event defined as death, end-stage renal disease, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. Secondary assessments included the time to the individual components of treatment failure and adverse events. MMF was superior to AZA with respect to the primary end point, time to treatment failure (hazard ratio, 0.44; 95% confidence interval, 0.25 to 0.77; P = 0.003), and with respect to time to renal flare and time to rescue therapy (hazard ratio, <1.00; P<0.05). Observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA. Adverse events, most commonly minor infections and gastrointestinal disorders, occurred in more than 95% of the patients in both groups (P = 0.68). Serious adverse events occurred in 33.3% of patients in the AZA group and in 23.5% of those in the MMF group (P = 0.11), and the rate of withdrawal due to adverse events was higher with AZA than with MMF (39.6% vs. 25.2%, P = 0.02).

Doses used in clinical studies

The doses of mycophenolate sodium (or the equivalent doses when administered as mycophenolate mofetil) used in the published clinical studies were varied.

Doses used for induction: In the pivotal 24-week ALMS study (Appel et al., 2009) the target dose of MMF was 3g per day (equivalent of 2.16g mycophenolate sodium or 720mg three times daily). The median dosage of MMF was calculated as 2.6g/day. In another 24-week published study (Ginzler et al.,2005), patients were treated with escalating doses of MMF up to 3g per day (equivalent of 2.16g mycophenolate sodium or 720mg three times daily). In this study the mean maximum tolerated dose of MMF was 2.68g per day (equivalent to 1.93g mycophenolate sodium or nearly 720mg three times daily).

Doses used for maintenance: In the pivotal long term maintenance study (Dooley et al., 2011), the target dose of MMF was 2g/day (equivalent to mycophenolate sodium 720mg twice daily); 80% of patients received a daily dose of 1.6mg or more.

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat toxicity

The hematopoietic and lymphoid system were the primary organs affected in toxicology studies conducted with mycophenolate sodium in rats and mice. Aplastic, regenerative anemia was identified as being the dose-limiting toxicity in MPA-exposed rodents. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) and a dose-dependent spleen enlargement and increase in extramedullary hematopoiesis. These effects occurred at systemic exposure levels which are equivalent to or less than the clinical exposure at the recommended dose of 1440 mg/day of Myfortic in renal transplant patients.

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

Reproductive toxicity

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

Carcinogenicity and, mutagenicity

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorigenic. The highest dose tested resulted in approximately 0.6 to 1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1440 mg/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 26-week oral carcinogenicity assay in a $P53^{\pm}$ (heterozygous) transgenic mouse model, mycophenolate sodium at daily doses up to 200 mg/kg was not tumorigenic. The highest dose tested, resulted in approximately 5 times the systemic exposure (plasma AUC) observed in renal transplant patients taking 1440 mg/day. The results of this study, however, remain equivocal because of the lack of a response to the positive control compound, benzene.

The genotoxic potential of mycophenolate sodium was determined in five assays. MPA was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay or the chromosomal aberration assay in human lymphocytes. The lowest dose showing genotoxic effects in a mouse bone marrow micronucleus resulted in approximately 3 times the systemic exposure (AUC or Cmax) observed in renal transplant patients at the tested clinical dose of 1440 mg of Myfortic per day. It is probable that the mutagenic activity observed was due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.

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 effects on female fertility were seen up to a dose of 20 mg/kg/day, a dose at which maternal toxicity and embryotoxicity were already observed.

PHARMACEUTICAL INFORMATION

Incompatibilities

Not applicable.

Storage

See folding box.

Myfortic should not be used after the date marked “EXP” on the pack.
Myfortic must be kept out of the reach and sight of children.

Instructions for use and handling

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

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

Special precautions for disposal

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

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