

MYFORTIC[®] (mycophenolic acid as sodium salt)

NAME OF THE MEDICINE

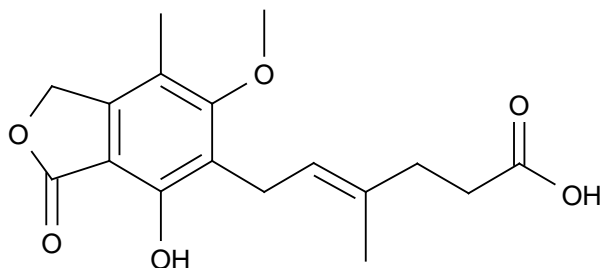
Active ingredient: Mycophenolic acid (as sodium salt)

Chemical Name: (E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-hex-4-enoic acid sodium salt

Empirical formula: C₁₇H₁₉O₆Na

Molecular weight: 342.32

Structural formula:



as the sodium salt

CAS Registry Number: 37415-62-6

DESCRIPTION

Mycophenolate sodium is the sodium salt of the active moiety, mycophenolic acid, and is a white to off-white, fine crystalline powder. It is freely soluble in aqueous media at physiological pH, as in the upper intestine, but practically insoluble in 0.1M HCl.

Each enteric-coated tablet contains 180 mg or 360 mg of mycophenolic acid (as the sodium salt), equivalent to 192.4 and 384.4 mycophenolate sodium.

Excipients: Starch-maize, povidone, crospovidone, lactose, silica-colloidal anhydrous, magnesium stearate. The enteric coating consists of: hypromellose phthalate, titanium dioxide, iron oxide yellow CI77492, indigo carmine CI73015 (180 mg tablet), iron oxide red CI77491 (360 mg tablet).

PHARMACOLOGY

Pharmacodynamics

Mycophenolic acid (MPA) is a non-nucleoside, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate limiting enzyme in the *de novo* synthesis pathway of guanosine triphosphate. Both T- and B-lymphocytes are highly dependent on this pathway for the generation of guanosine nucleotides whereas non-lymphoid cells can utilise a salvage pathway for the generation of guanosine triphosphate. MPA selectively decreases the lymphocyte nucleotide pool, which effectively impairs the capacity

of T- and B-lymphocytes to proliferate. MPA inhibits glycosylation of adhesion molecules on lymphocytes and monocytes (a process requiring guanosine triphosphate). This action could potentially decrease the recruitment of lymphocytes and monocytes into sites of chronic inflammation, an important process in ongoing rejection.

PHARMACOKINETICS

Absorption:

Following oral administration, mycophenolate sodium is extensively absorbed. The median time to maximum MPA plasma concentration (t_{max}) is 2 hours (Table 1) but there is significant variability, especially with food, with values up to 16 hours fasting and 24 hours fed. *In vitro* studies demonstrated that the enteric-coated formulation of Myfortic prevents the release of MPA under acidic condition, as in the stomach.

In stable renal transplant patients on cyclosporin (Neoral[®]) based immunosuppression, the mean absolute bioavailability of Myfortic tablets was 71% (range: 38-98%). Myfortic pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2160 mg. Compared to the fasting state, administration of Myfortic 720 mg with a high fat meal had no effect on the systemic exposure (AUC) of MPA, which is the most relevant pharmacokinetic parameter linked to efficacy. However, there was a 33% decrease in the maximal plasma concentration (C_{max}) of MPA and a delay in t_{max} when Myfortic was given with a high fat meal.

Distribution:

The volume of distribution at steady state for MPA is 50 litres. Both MPA and its major metabolite, mycophenolic acid glucuronide (MPAG), are highly protein bound, 97% and 82%, respectively. The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminaemia, concomitant use of drugs with high protein binding) and this may put patients at increased risk of MPA-related adverse effects.

Metabolism:

The half life of MPA (mean \pm SD) is 11.7 ± 3.2 hours and the clearance (mean \pm SD) is 8.4 ± 1.8 L/hr. MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide. MPAG is the predominant metabolite of MPA and is pharmacologically inactive. In stable renal transplant patients on Neoral based immunosuppression, approximately 28% of the oral Myfortic dose is converted to MPAG by presystemic metabolism. The half-life of MPAG (mean \pm SD) is approximately 15.7 ± 3.9 hours and its clearance (CL/f_m) is about 0.45 ± 0.15 L/hr (mean \pm SD).

Excretion:

Although negligible amounts of MPA are present in the urine (<1%), 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 6-8 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 cyclosporin based immunosuppression:

Table 1 shows the mean pharmacokinetic parameters for MPA following administration of Myfortic. In the early post transplant period, mean MPA AUC and mean MPA C_{max} were approximately one-half of that measured six months post transplant.

Table 1: Mean (SD) pharmacokinetic parameters for MPA following oral administration of Myfortic to renal transplant patients on Neoral based immunosuppression

| | Adult single dose n = 24 | Adult multiple dose x 6 days, BID n=12 | Adult multiple dose x 28 days, BID n=36 | Adult chronic, multiple dosing BID n=48 | | |
|---------------------------------|-----------------------------|---|--|--|-------------|-------------|
| | | | | Post Transplant | | |
| | | | | 14 days | 3 months | 6 months |
| Dose (oral) | 720 mg | 720 mg | 720 mg | 720 mg | 720 mg | 720 mg |
| T_{max} (median) | 2 hrs | 2 hrs | 2.5 hrs | 2 hrs | 2 hrs | 2 hrs |
| C_{max} (ug/mL) | 26.1 (12.0) | 37.0 (13.3) | 31.2 (18.1) | 13.9 (8.6) | 24.6 (13.2) | 23.0 (10.1) |
| AUC 0-∞ (ug*hr/mL) | 66.5 (22.6) | - | - | - | - | - |
| AUC 0-12 (ug*hr/mL) | - | 67.9 (20.3) | 71.2 (26.3) | 29.1 (10.4) | 50.7 (17.3) | 55.7 (14.6) |

Pharmacokinetics in special patient groups:

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

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

Impaired renal function: There are no data for Myfortic. After a single dose of mycophenolate mofetil containing an equivalent amount of MPA to 720 mg of Myfortic, clearance of MPA appeared to be reduced with increasing levels of renal impairment. The area under the MPA plasma concentration – time curve (MPA exposure) increased by up to 30% in patients with mild to moderate renal impairment (GFR 25-80 mL/min/1.73m²) and 75% in patients with severe renal impairment (GFR < 25 mL/min/1.73m²). However, there

was considerable variability and small numbers of subjects (6-7 at each level of renal impairment). MPAG exposure was 3 to 6-fold higher in subjects with moderate to severe renal impairment, which was consistent with renal elimination of MPAG.

At higher MPAG concentrations (observed in patients with renal impairment or delayed graft function), plasma protein binding of MPA may be reduced as a result of competition between MPAG and MPA for binding sites. This would result in increased free MPA in plasma.

Impaired hepatic function: There are no data for Myfortic. After a single dose of mycophenolate mofetil equivalent to 720 mg MPA in patients 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 TRIALS

Renal transplant

Two multi-centre, randomised, double-blind, parallel group studies were conducted in renal transplant patients. The first study was conducted in newly transplanted patients and in the second study, maintenance renal transplant patients were randomised 1:1 to either remain on mycophenolate mofetil (MMF) or be switched to Myfortic. Both pivotal studies were reference therapy-controlled clinical studies using commercially marketed MMF as the comparator.

De novo Renal Transplant Patients

A total of 423 patients were randomised within 48 hours of renal transplantation, 213 to Myfortic (1.44 g/ day, 720 mg bid) and 210 to MMF (2 g/day, 1 g bid) as part of triple immunosuppressive therapy with Neoral and steroids. The aim of the study was to show therapeutic equivalence of Myfortic to MMF as measured by the incidence of biopsy-proven acute rejection, graft loss, death or lost to follow-up at 6 and 12 months of treatment. All patients contributed data at 6 and 12 months. Efficacy results are reported in Table 2 for the intent-to-treat population. Similar results were obtained for the per protocol analysis – an analysis which excluded patients with serious protocol violations.

Table 2: Analysis of primary efficacy endpoint and its components at 6 and 12 months (Study ERL B301)

| | Myfortic 1.44 g/day (n = 213) | MMF 2 g/day (n = 210) | 95% CI ERL-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 (Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up at Month 6) was entirely contained in the interval (-12%, 12%).

Maintenance Renal Transplant Patients

A total of 322 patients who were at least 6 months post-renal transplant and stabilised on 2 g MMF and Neoral, were randomised, 159 to Myfortic (1.44 g/ day, 720 mg bid) and 163 to MMF (2 g/day, 1 g bid) plus Neoral, with or without steroids. The primary objective was to demonstrate safety and tolerability of Myfortic compared to MMF and this objective was met. Evaluation of efficacy was a secondary objective. The incidence rate of biopsy-proven acute rejection, graft loss, death or lost to follow-up, and the incidence of suspected or biopsy-proven acute rejections within 6 and 12 months post-randomisation, were compared across treatment groups. All patients contributed data at 6 months, and 223 patients contributed data at 12 months. Efficacy results are shown in Table 3.

Table 3: 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 biopsy-proven acute rejection, graft loss or death.

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 ($88.4 \mu\text{mol/L}$), 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 $\geq 50\%$ 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 SLEDAI 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.

INDICATIONS

- Myfortic is indicated 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 WHO Class III, IV or V lupus nephritis.

This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.

CONTRAINDICATIONS

Myfortic is contraindicated in pregnancy since it is associated with increased risks of first trimester pregnancy loss and congenital malformations (see “PRECAUTIONS – Use in pregnancy”). Females of reproductive potential must be counselled regarding pregnancy prevention and planning.

It is also contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients of the formulation (see “DESCRIPTION”).

PRECAUTIONS

Embryofetal toxicity

Myfortic can cause foetal harm when administered to a pregnant woman. Use of Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

Women of child-bearing potential

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

Women of child-bearing potential must use highly effective contraception. Two types of reliable contraception should start before beginning Myfortic therapy, during therapy and for six weeks after their last dose of Myfortic. Given that mycophenolate mofetil reduces blood levels of the hormones in the oral contraceptive pill, it is possible that Myfortic could reduce the efficacy of oral contraceptives (see “PRECAUTIONS, Interactions with other medicines”).

Pregnancy and breast-feeding, fertility and male patients

For information on use in pregnancy, breast-feeding and contraceptive requirements see sections entitled “Use in pregnancy”, “Use in lactation”, “Women of child-bearing potential”, “Effects on fertility” and “Male patients”.

Myfortic should not be used during breast-feeding (see section entitled “Use in lactation”).

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 “ADVERSE EFFECTS”). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. In order to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections:

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

Oversuppression of the immune system increases the susceptibility to infection, including opportunistic infections, fatal infections and sepsis (see “ADVERSE EFFECTS”).

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives which include mycophenolate mofetil (MMF) and mycophenolate sodium (see “ADVERSE EFFECTS”). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. Mycophenolate mofetil is metabolized to mycophenolic acid, the active ingredient in Myfortic and the active form of the drug. 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 “ADVERSE EFFECTS”). Consideration should be given to reducing the total immunosuppression in patients who develop PML or PVAN. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Blood dyscrasias:

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anaemia, see “ADVERSE EFFECTS”), 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 dyscrasias occur (e.g. neutropenia with absolute neutrophil count $<1.5 \times 10^9/L$ or anaemia), it may be appropriate to interrupt or discontinue Myfortic.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents (see “ADVERSE EFFECTS”). MMF is metabolised to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. 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 minimise the risk of graft rejection.

Vaccinations:

Patients should be advised that, during treatment with MPA, vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see “PRECAUTIONS-Interactions with other medicines”). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal disorders:

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.

Patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT):

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

Male patients

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

Effects on fertility:

Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 18 mg/kg/day. The systemic exposure to MPA (plasma AUC) at this dose represents approximately 2 times the clinical exposure at the recommended dose of 1.44 g/day. No effects on female fertility were seen up to a dose of 20 mg/kg/day, a dose at which embryotoxicity was observed, with estimated systemic exposure to MPA (plasma AUC) approximately 3 times clinical exposure.

Use in pregnancy (Category D):

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. Following oral or IV administration, MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. In the US National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In post-marketing data (collected from 1995 to 2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

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.

Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed with mycophenolate sodium or mycophenolate mofetil during organogenesis. In a teratology study performed with mycophenolate sodium in rats at 1 mg/kg/day (the lowest dose tested), there was an increase in resorptions, and malformations in the offspring were observed including anophthalmia, exencephaly and umbilical hernia. The estimated systemic exposure to MPA at this dose is about 0.1 times the clinical exposure (plasma AUC) at the recommended dose of 1.44 g/day.

Use in lactation:

It is not known whether MPA is excreted in human milk but studies in rats given radiolabelled mycophenolate mofetil have shown the excretion of radioactivity into milk.

Myfortic should not be used during lactation.

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

Paediatric use:

Safety and efficacy in paediatric patients have not been established.

Genotoxicity:

Mycophenolate sodium and mycophenolate mofetil were genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells *in vitro* and in the *in vivo* mouse micronucleus assay. They were not genotoxic in the bacterial mutation assay. Mycophenolate sodium showed weak evidence of genotoxicity in the chromosome aberration assay in human lymphocytes. There were no relevant qualitative or quantitative differences in the genotoxic potential of mycophenolate sodium and mycophenolate mofetil. The genotoxic activity of MPA may be due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.

Carcinogenicity:

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 0.6-1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 26-week oral carcinogenicity assay in a P53[±] (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 1.44 g/day. The results of this study, however, remain equivocal because of the lack of a response to the positive control compound, benzene.

In a 2-year carcinogenicity study in rats, administration of oral doses of 6 and 9 mg/kg/day mycophenolate sodium resulted in an increase in the incidence of benign thymomas in the thymus in females. Systemic exposure (plasma AUC) at these respective doses was about 0.5 and 1 times that observed in renal transplant patients taking 1.44 g/day.

Effects on ability to drive and use machinery:

No studies on the effects of Myfortic 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.

INTERACTIONS WITH OTHER MEDICINES

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte globulin, basiliximab, cyclosporin and corticosteroids. The efficacy and safety of the use of Myfortic with other immunosuppressive agents have not been studied.

Oral contraceptives: Concomitant use of Myfortic with oral contraceptives has not been studied. Oral contraceptives undergo oxidative metabolism while Myfortic is metabolised by glucuronidation. Given the different metabolism of Myfortic and oral contraceptives, no drug interaction between these two classes of drug is expected. However, in a drug-drug interaction study, mean levonorgestrel AUC was decreased by 15% when coadministered

with mycophenolate mofetil. Therefore, it is recommended that oral contraceptives are coadministered with Myfortic with caution and additional birth control methods be considered (see PRECAUTIONS Section – “Women of child-bearing potential” and “Male patients”).

Azathioprine: It is recommended that Myfortic should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

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

Aciclovir: Concomitant use of Myfortic with aciclovir has not been studied. After co-administration of mycophenolate mofetil (which delivers MPA to the systemic circulation) and aciclovir, higher plasma concentrations of MPAG and aciclovir have been observed compared with administration of each drug alone. In renal impairment, the two drugs may compete for tubular secretion resulting in further increases in MPAG and aciclovir plasma concentration. In this situation, patients should be carefully monitored.

Cyclosporin: When studied in stable renal transplant patients, cyclosporin (Neoral) pharmacokinetics were unaffected by steady state dosing of Myfortic.

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 determined during concomitant cyclosporin (Neoral) and tacrolimus (Prograf®) treatments. Mean MPA AUC was 19% higher and C_{max} about 20% lower, and mean MPAG AUC and C_{max} were about 30% lower on tacrolimus treatment compared to Neoral treatment.

Conditions of decreased protein binding sites: MPA concentration may increase under conditions of decreased protein binding sites, which may occur when Myfortic is administered concomitantly with highly protein bound drugs and/or in the setting of uraemia. This may put patients at increased risk of MPA-related adverse effects.

Gastroprotective agents:

Antacids with magnesium and aluminium hydroxides: The absorption of Myfortic was decreased when administered with antacids containing magnesium and aluminium hydroxide, resulting 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 concomitant administration of Myfortic and pantoprazole given at 40 mg twice daily during the four previous days.

Cholestyramine and drugs that interfere with enterohepatic circulation: Due to its capacity to block the enteric circulation of drugs, cholestyramine may decrease the systemic exposure of MPA. Caution should be used when co-administering cholestyramine or drugs that interfere with enterohepatic circulation because of the potential to reduce the efficacy of Myfortic.

ADVERSE EFFECTS

Adverse effects from clinical trials in renal transplant patients

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 "PRECAUTIONS-Development of malignancies"). 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 2 *de novo* patients (0.9%) and 3 maintenance patients (1.9%) 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 increases with total immunosuppressive load (see "PRECAUTIONS-Development of infections"). 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 one year were CMV, candidiasis and herpes simplex. The overall rate of CMV infections (serology, viraemia or disease) observed in Myfortic clinical trials was 21.6% in *de novo* and 1.9% in maintenance renal transplant patients.

Other adverse drug reactions:

Table 4 below contains adverse drug reactions, possibly or probably related to Myfortic, reported in the two phase III randomised, double blind, controlled, multi-centre trials: 1 in *de novo* renal transplant patients and 1 in maintenance renal transplant patients, in which Myfortic was administered at a dose of 1440 mg /day for 12 months together with cyclosporin

microemulsion (Neoral) and corticosteroids. It is compiled according to MedDRA system organ class.

Adverse reactions are listed according to the following categories:

Very common $\geq 10\%$ ($\geq 1/10$)

Common $\geq 1\%$ and $< 10\%$ ($\geq 1/100$ and $< 1/10$)

Uncommon $\geq 0.1\%$ and $< 1\%$ ($\geq 1/1000$ and $< 1/100$)

Rare $\geq 0.01\%$ and $< 0.1\%$ ($\geq 1/10000$ and $< 1/1000$)

Very rare $< 0.01\%$ ($< 1/10000$)

Table 4

| Body system | Incidence | Adverse reaction |
|--|-----------------------------------|---|
| Infections and infestations | Very common Common Uncommon | Viral, bacterial and fungal infections Upper respiratory tract infections, pneumonia Wound infection*, sepsis*, osteomyelitis* |
| Blood and lymphatic system disorders | Very common Common Uncommon | Leukopenia Anaemia, thrombocytopenia Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy* |
| Nervous system disorders | Common Uncommon | Headache Tremor, insomnia* |
| Respiratory, thoracic and mediastinal disorders | Common Uncommon | Cough Pulmonary congestion, wheezing |
| Gastrointestinal disorders | Very common Common Uncommon | Diarrhoea Abdominal distension, abdominal pain, abdominal tenderness, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting 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 Uncommon | Fatigue, pyrexia Influenza like illness, oedema lower limb*, pain, rigors*, thirst* weakness* |
| Metabolism and nutrition disorders | Uncommon | Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia, hypophosphataemia* |
| Skin and cutaneous tissue disorders | Uncommon | Alopecia, contusion* |
| Hepato-biliary disorders | Common | Abnormal hepatic function tests |
| Cardiac disorders | Uncommon | Tachycardia, pulmonary oedema*, ventricular extrasystoles* |
| Eye disorders | Uncommon | Conjunctivitis*, blurred vision* |

| | | |
|---|--------------------|---|
| Musculoskeletal, connective tissue and bone disorders | 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 | Uncommon | Abnormal dreams*, delusional perception* |
| Renal and urinary disorders | Common Uncommon | Increased blood creatinine Hematuria*, renal tubular necrosis*, urethral stricture |
| Reproductive system and breast disorders | Uncommon | Impotence* |

* Events reported in a single patient only.

Renal transplant patients were treated with 1440 mg Myfortic daily up to one year. A similar profile was seen in the *de novo* and maintenance transplant population although the incidence tended to be lower in the maintenance patients.

Elderly patients:

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression. Elderly patients receiving Myfortic as part of a combination immunosuppressive regimen did not show an increased risk of adverse reactions compared to younger individuals in the Myfortic clinical trials.

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

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

Adverse effects from post marketing experience

Rash has been identified as an adverse effect from post-approval clinical trials, post marketing surveillance and spontaneous reports.

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

Congenital malformations have been reported in offspring of patients exposed to mycophenolate mofetil (MMF) during pregnancy (see PRECAUTIONS, Use in pregnancy).

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 “PRECAUTIONS”).

Blood and lymphatic system disorders: 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 “PRECAUTIONS”).

Gastrointestinal disorders: colitis, oesophagitis (including CMV-colitis and -oesophagitis), CMV gastritis, pancreatitis, intestinal perforation, gastrointestinal haemorrhage, gastric ulcers, duodenal ulcers, ileus.

DOSAGE AND ADMINISTRATION

Treatment with Myfortic should be initiated and maintained by appropriately qualified specialists who are expert in managing the safety risks associated with the contraindication for use in pregnancy. Consideration should be given to therapeutic drug monitoring of mycophenolate because of the variable pharmacokinetic profile and narrow therapeutic margin.

Myfortic should not be initiated in women of child-bearing potential until a negative pregnancy test has been obtained. For information on use in pregnancy and contraceptive requirements see sections entitled “Women of child-bearing potential”, “Use in pregnancy”, and “Male patients”).

A dose of 1440mg/day of mycophenolate sodium has been shown to be equivalent to 2 g/day of mycophenolate mofetil. Myfortic and CellCept (mycophenolate mofetil) should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Myfortic tablets should not be crushed and should be swallowed whole. Patients should be advised to take Myfortic consistently either with or without food, but not switch between fed and fasted states because of the risk of increased MPA AUC variability.

Renal transplant patients:

Myfortic should be initiated in *de novo* patients within 48 hours following transplantation. The recommended dose is 720 mg administered twice daily (1440 mg daily dose).

Paediatric patients:

Safety and efficacy in paediatric patients have not been established

Elderly patients:

No dose adjustment is required in elderly patients.

Patients with renal insufficiency:

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. Patients with severe chronic renal impairment (glomerular filtration rate < 25 ml·min⁻¹·1.73 m⁻²) should be carefully monitored.

Patients with hepatic insufficiency:

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

Treatment during rejection episodes:

Dosage reduction or interruption of Myfortic is not required during episodes of renal transplant rejection.

Lupus nephritis patients:

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

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

OVERDOSAGE

Signs and symptoms:

There has been no reported experience of overdosage of Myfortic in humans.

Treatment:

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. By interfering with enterohepatic circulation of MPA, bile acid sequestrants such as cholestyramine may reduce the systemic exposure of MPA.

Contact Poison Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentation:

Myfortic 180 mg:

Lime green, enteric-coated, round tablet with bevelled edges and the imprint “C” on one side.

Myfortic 360 mg:

Pale orange red, enteric-coated, ovaloid tablet with imprint 'CT' on one side.

Packs containing 50 or 120 tablets.

Storage conditions:

Store in original package and container below 30°C. Protect from moisture and light. Keep out of reach of children.

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

25 March 2003 (180mg tablet); 26 March 2003 (360mg tablet)

DATE OF MOST RECENT AMENDMENT

7 September 2012

For internal use only:

(myf030912i) based on CDS 18 July 2011.