AUSTRALIAN PRODUCT INFORMATION

CEPTOLATE

Mycophenolate mofetil

1 NAME OF THE MEDICINE

Mycophenolate mofetil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEPTOLATE 250 mg capsules contain 250 mg of mycophenolate mofetil (MMF).

CEPTOLATE 500 mg tablets contain 500 mg of mycophenolate mofetil.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

CEPTOLATE 250 mg capsules - caramel opaque cap/lavender opaque body, hard shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with "MYLAN" over "2250" in black ink on both the cap and body.

CEPTOLATE 500 mg tablets - light pink film coated, oval, biconvex, bevelled edge tablet debossed with "MYLAN" on one side of the tablet and "472" on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CEPTOLATE (mycophenolate mofetil) is indicated for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants.

CEPTOLATE (mycophenolate mofetil) is indicated for the prophylaxis of organ rejection in paediatric patients with a body surface area of ($\geq 1.25\ m^2$) receiving allogeneic renal transplants (see section 4.2 Dose and Method of Administration).

4.2 DOSE AND METHOD OF ADMINISTRATION

The initial dose of MMF should be given as soon as clinically feasible following transplantation. Intravenous administration is recommended in those patients unable to take oral medication. However, oral administration should be initiated as soon as possible.

Please note that CEPTOLATE mycophenolate mofetil in not available in the intravenous dosage form.

Adults

Renal Transplantation

The recommended dose in renal transplant patients is 1 g administered orally twice daily (2 g daily dose).

Cardiac Transplantation

The recommended dose in cardiac transplant patients is 1.5 g administrated orally twice daily (3 g daily dose).

Hepatic Transplantation

The recommended dose in hepatic transplant patients is 1.5 g administered orally twice daily (3 g daily dose).

Other Transplants

The recommended dose in other transplants is 2 to 3g per day depending on the level of immunosuppression required.

Paediatric Patients (≥ 1.25 m^2)

MMF capsules and tablets are not suitable for paediatric patients whose body surface area is < 1.25 m^2. Patients with a body surface area of 1.25 m^2 to 1.5 m^2 may be dosed with MMF capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area > 1.5 m^2 may be dosed with MMF capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

MMF may be administered in combination with ciclosporin and corticosteroids.

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (ANC < $1.3x10^9$/L), dosing with MMF should be interrupted, or the dose should be reduced, and the patient carefully observed (see section 4.4 Special Warnings and Precautions for Use). Patients should be advised to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

In renal transplant patients with severe chronic renal impairment (GFR < 25 mL/min/1.73m²) outside of the immediate post-transplant period, doses of MMF greater than 1 g administered twice a day should be avoided. No data are available in cardiac or hepatic allograft recipients with severe chronic renal impairment. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal allograft function post-operatively.

No dosage adjustment is required in the elderly or in renal transplant patients with hepatic parenchymal disease.

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

4.3 CONTRAINDICATIONS

Allergic reactions to MMF have been observed, therefore, MMF is contraindicated in patients with a hypersensitivity to MMF or to mycophenolic acid.

MMF is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see section 4.6 Fertility, Pregnancy and Lactation).

MMF is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see section 4.6 Fertility, Pregnancy and Lactation).

MMF is contraindicated in women who are breastfeeding (see section 4.6 Fertility, Pregnancy and Lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Female patients of childbearing potential must use effective contraception before, during and for six weeks after receiving MMF. MMF is contraindicated during pregnancy and during breastfeeding (see section 4.6 Fertility, Pregnancy and Lactation).

Men should not donate semen during therapy and for 90 days following discontinuation of MMF.

Neoplasms

As with other patients receiving immunosuppressive regimes involving combinations of medicines, patients receiving MMF as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than the use of any specific agent. Approximately 1% of patients receiving MMF with other immunosuppressive agents in the controlled studies of prevention of rejection have developed

lymphoproliferative disease or lymphoma. As immunosuppression increases the risk of skin cancer, patients should also be advised to limit their exposure to sunlight and other sources of UV light by wearing protective clothing and using sunscreen with a high protection factor.

Infections

Over suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis. In the controlled studies for the prevention of rejection, the incidence of fatal infection was similar in patients receiving MMF or control therapy in combination with other immunosuppressive agents. There was a higher incidence of fatal infection in the liver transplant study (5%) compared with the other studies (2%).

Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of progressive multifocal leukoencephalopathy (PML), associated with the JC virus, sometimes fatal, have been reported in MMF-treated patients. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function. 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. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BK virus-associated nephropathy has been observed during the use of MMF in patients post-renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk of BK virus-associated nephropathy. Due to the cytostatic effect of MMF on B- and T-lymphocytes, increased severity of COVID-19 may occur. Dose reduction or discontinuation of MMF should be considered for patients who develop evidence of BK virus-associated nephropathy, or in cases of clinically significant COVID-19.

Blood and Immune System

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients however, reduced immunosuppression may place the graft at risk.

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

Patients on MMF should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF, concomitant medications, viral infection or some combination of these causes. If neutropenia develops (absolute neutrophil count < 1.3 x $10^3/\mu L$), dosing with MMF should be interrupted, or the dose reduced, and the patient should be carefully observed.

0.5% of patients receiving MMF 2 g for prevention of rejection in renal transplantation, 2.8% of patients receiving MMF 3 g in cardiac transplantation and 3.6% of patients receiving MMF 3 g in hepatic transplantation, developed severe neutropenia (absolute neutrophil count [ANC] < $5x10^8/L$).

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

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of MMF.

Gastrointestinal

As MMF has been associated with an increased incidence of digestive system adverse events, including uncommon cases of gastrointestinal tract ulceration, haemorrhage, and perforation (colon, gall bladder) in post-marketing surveillance, MMF should be administered with caution in patients with active serious digestive system disease. Gastrointestinal tract bleeding (requiring hospitalisation) has been observed in approximately 1.4% of patients treated with MMF 2 g in renal transplantation, 2.8% of patients receiving 3 g in cardiac transplantation and in 5.4% of patients receiving MMF 3 g in hepatic transplantation. Gastrointestinal tract perforations have rarely been observed. Most patients were also receiving other drugs that are associated with these complications (see section 4.8 Adverse Effects (Undesirable Effects)). It should be noted that patients with active peptic ulcer disease were excluded from enrolment in studies with MMF.

Since MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, 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.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants which interfere with MPA enterohepatic recirculation e.g. ciclosporin , to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle e.g. colestyramine, antibiotics should be used with caution due to their potential to reduce the plasma levels and efficacy of MMF (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

Azathioprine: It is recommended that MMF should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied.

Use in Renal Impairment

Patients with severe chronic renal impairment (GFR < 25 mL/min/1.73m^2) who have received single doses of MMF showed increased plasma AUCs of MPA and MPAG relative to patients with lesser degrees of renal impairment or normal healthy patients. Patients with severe chronic renal impairment should be carefully monitored and administration of doses of MMF greater than 1g twice daily should be avoided (see section 4.2 Dose and Method of Administration and section 5.2 Pharmacokinetic Properties).

In patients with delayed graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2 – 3-fold higher, compared to that seen in post-transplant patients without delayed graft function. In the three controlled studies of prevention of rejection, there were 298 of 1 483 patients (20%) with delayed graft function. Although patients with delayed renal allograft function have a higher incidence of certain adverse events (anaemia, thrombocytopenia, hyperkalaemia) than patients without delayed graft function, these events were not more frequent in patients receiving MMF than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed.

In renal transplant patients with severe chronic renal impairment, administration of doses greater than 1 g twice daily should be avoided.

Paediatric Use

Based on a safety and pharmacokinetics study in renal paediatric patients, no significant differences in pharmacokinetic parameters in comparison to adult patients were observed. Paediatric patients experienced a

higher incidence of certain adverse events (see section 4.8 Adverse Effects (Undesirable Effects)). Data are insufficient to establish safety and efficacy in children below the age of two years.

Use in the Elderly

Elderly patients may be at an increased risk of adverse events such as certain infections (including CMV tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals. Elderly patients (over 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Pharmacokinetic behaviour of MMF in the elderly has not been formally evaluated.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug interaction studies with MMF have been conducted with aciclovir, antacids, belatacept, colestyramine, ciclosporin , ganciclovir, oral contraceptives, proton pump inhibitors, sirolimus, telmisartan, tacrolimus and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other medicines that may be commonly administered to renal, cardiac or hepatic transplant patients.

Aciclovir: Following single dose administration of MMF (1 g) and aciclovir (800 mg) to normal healthy subjects, higher MPAG (8.6%) and aciclovir (17.4%) plasma AUCs were observed when MMF was administered with aciclovir in comparison to the administration of each drug alone. As MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for the mycophenolate and aciclovir or its prodrugs e.g. valaciclovir to compete for tubular secretion and thus further increases in concentrations of both drugs may occur.

Antacids with magnesium and aluminium hydroxides: Absorption of a single dose of MMF (2.0 g) was decreased when aluminium/magnesium hydroxide antacids were administered concomitantly to rheumatoid arthritis patients. The C_{max} and 24-hour AUC values for MPA were 33% and 17% lower respectively, than when MMF was administered alone under fasting conditions.

Antibiotics: Antibiotics eliminating β-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning the following antibiotics is available:

Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tended to diminish with continued antibiotic use and cease after discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

Norfloxacin and metronidazole: The combination of norfloxacin and metronidazole reduced the MPA AUC following a single dose of MMF.

Trimethoprim and sulfamethoxazole: Following single dose administration of MMF (1.5 g) to healthy male volunteers pre-treated for 10 days with trimethoprim 160 mg/sulfamethoxazole 800 mg, no effect on the bioavailability of MPA was observed.

Colestyramine: Following single dose administration of 1.5 g MMF in normal healthy subjects pre-treated with 4 g three times daily of colestyramine for 4 days, there was a mean 40% reduction in the AUC of MPA (see section 5.2 Pharmacokinetic Properties). In view of the significant reduction in the AUC of MPA by colestyramine, caution should be used with the concomitant use of MMF and any drug which interferes with enterohepatic circulation because of the potential to reduce the efficacy of MMF.

Ciclosporin : Ciclosporin pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.0 g MMF twice daily in stable renal transplant patients. The mean (± SD) dose normalised $AUC_{0\text{-}12h}$ of MPA after 14 days and 3 months of multiple doses of MMF and ciclosporin in 17 renal transplant patients were 43 ± 11µg.h/mL.g and 56 ± 31µg.h/mL.g, respectively. However, ciclosporin interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with MMF and ciclosporin compared with patients receiving sirolimus or belatacept and similar doses of MMF. Conversely, changes of MPA exposure should be expected when switching patients from ciclosporin to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle.

Drugs affecting glucuronidation: Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA $AUC_{0\text{-}\infty}$ by 35% was observed with concomitant administration of isavuconazole). Caution is therefore recommended when administering these drugs concomitantly with MMF.

Telmisartan: Concomitant administration of telmisartan and MMF resulted in an approximately 30% decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and activity.

Sirolimus: A study in 36 renal transplant patients demonstrated that concomitant administration of MMF (1 g twice daily) and sirolimus resulted in the mean (± SD) $AUC_{0\text{-}12h}$ of MPA after 14 days and 3 months were 81 ± 36 and 71 ± 26 µg.h/mL.g respectively. Another study using 45 renal transplant patients demonstrated that a significant proportion of patients (10 of 30) who received the combination of sirolimus and MMF were withdrawn with symptoms consistent with MPA or sirolimus toxicity.

Monitoring of MPA levels should be performed in renal graft recipients co-treated with sirolimus because of the risk of overexposure to this immunosuppressive agent.

Ganciclovir: Following single dose administration in stable renal transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and IV ganciclovir (5 mg/kg). However, as MPAG plasma and ganciclovir concentrations are increased in the presence of renal impairment, the potential exists for the two medicines to compete for tubular secretion, and thus further increases in concentrations of both medicines may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrugs (e.g. valganciclovir) are co-administered, patients should be carefully monitored. However, with MPA no substantial alteration of MPA pharmacokinetics is anticipated and dose adjustment of MMF is not required.

Iron: In a study involving 16 healthy volunteers, no clinically relevant interaction was found between MMF and iron supplements when administered in a fasting state. In the same study, a 15% reduction in MPA AUC was observed when MMF and iron were administered simultaneously with food. In an earlier study involving 7 healthy volunteers, a significant reduction in MPA AUC was observed when MMF and iron were administered in a fasting state. To avoid any possible interactions, iron supplements should be administered at least 3 hours following MMF.

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

Oral contraceptives: A study of co-administration of MMF (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 - 0.04 mg) and levonorgestrel (0.05 - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 - 0.1 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of MMF on serum levels of progesterone, LH and FSH, thus indicating no influence of MMF on the ovulation-suppressing action of the oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of MMF (see section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy).

Proton Pump Inhibitors (PPIs): Decreased MPA exposure has been observed when PPIs, including lansoprazole and pantoprazole, were administered with MMF. The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has

not been established, PPIs should be used with caution when co-administered to transplant patients being treated with MMF.

Rifampicin: After correction for dose, a 70% decrease in MPA exposure (AUC_{0-12h}) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust MMF doses accordingly to maintain clinical efficacy when the drugs are administered concomitantly.

Tacrolimus: The AUC and C_{max} of MPA, the active metabolite of MMF, were not significantly affected by co-administration with tacrolimus, in stable hepatic transplant patients initiated on MMF and tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of MMF (1.5g twice daily) were administered to patients taking tacrolimus.

However, in renal transplant patients, tacrolimus concentration did not appear to be altered by MMF.

Sevelamer and other calcium-free phosphate binders: Concomitant administration of sevelamer and MMF in adults and paediatric patients decreased the C_{max} and AUC $_{0-12}$ of MPA by 30% and 25% respectively. There are no data on MMF with phosphate binders other than sevelamer. This data suggest that sevelamer and other calcium-free phosphate binders should preferentially be given two hours after MMF intake to minimise impact on the absorption of MPA.

Other interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with MMF in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other medicines known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

MMF had no effect on fertility of male rats at oral doses up to 20 mg/kg/day or on female rats at oral doses up to 4.5 mg/kg/day (0.8 and 0.1 times the expected maximum clinical dose based on AUC values respectively). A female fertility and reproduction study conducted in rats caused malformations (see section 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy below). Malformations (including anophthalmia, agnathia and hydrocephaly) occurred in the first-generation offspring of female rats treated with oral doses of MMF in the absence of maternal toxicity. No effect was seen on the fertility of male rats treated with MMF.

Use in Pregnancy

Pregnancy category: D

MMF is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods due to its mutagenic and teratogenic potential (see section 4.3 Contraindications). MMF is a human teratogen with an increased risk of spontaneous abortions (mainly in the first trimester) and congenital malformations in case of maternal exposure during pregnancy (see section 4.8 Adverse Effects (Undesirable Effects)). In the medical literature, the risk of spontaneous abortions has been reported at 45% to 49% following MMF exposure, compared to a reported rate between 12% and 33% in solid organ transplant patients treated with other immunosuppressants.

Congenital malformations (including multiple malformations in individual newborns) have been reported in 23% to 27% of live births in MMF exposed pregnancies in published literature. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than MMF.

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

These findings were consistent with teratology studies performed in rats and rabbits where fetal resorptions and malformations occurred in absence of maternal toxicity.

Embryofoetal development studies were conducted with MMF in rats (0.6, 2, 6 mg/kg/day on gestation days 7-16, and 0.5, 1.5 and 4.5 mg/kg/day from prior to conception to weaning) and rabbits (10, 30, 90 mg/kg/day on gestation days 7-19). Foetal resorptions and malformations occurred in rats at doses of 4.5mg/kg/day or more (0.1 times the expected maximum human dose based on AUC values) and in rabbits at 90 mg/kg/day (0.1 times the expected maximum human dose based on AUC values), in the absence of maternal toxicity.

The observed malformations in rats or rabbits were highly predictive of human malformations. Animal malformations with reported human correlates can be broadly classified as facial defects (including cleft palate, agnathia), eye abnormalities (including anopthalmia, micropthalmia), cardiac malformations (including ectocardia), nervous system malformations (including hydrocephaly), abdominal and thoracic wall defects (including umbilical and diaphragmatic hernia), kidney and lung defects (including renal agenesis, ectopic kidney and lung hypoplasia), reproductive organ defects (cryptorchidism) and skeletal malformations. Additional animal malformations included spleen and adrenal gland defects (aplasia, dysplasia).

The no-effect levels for teratogenicity in rats and rabbits were 2 and 30 mg/kg/day, respectively. A peri and postnatal study in rats administered MMF 1, 3 or 10 mg/kg/day from gestation day 17 to weaning showed no adverse effects.

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counselled regarding pregnancy prevention, and planning.

Pregnancy Testing

Prior to starting therapy with MMF, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting MMF. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.

Contraception

Females

Women of child bearing potential should use two reliable forms of contraception simultaneously, including at least one of which must be highly effective, before beginning MMF therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Males

Limited clinical evidence is currently available on paternal exposure to MMF.

Non-clinical evidence shows that the dose of mycophenolate that could be transferred via the seminal fluid to a potentially pregnant partner is 30-fold lower than the concentration without teratogenic effects in rats, and 200-fold lower than the lowest teratogenic concentration in rats. Therefore, the risk of harm mediated via seminal fluid is considered negligible. However, genotoxic effects have been observed in animal studies at exposures exceeding the human therapeutic exposures by approximately 2.5-times. Thus, the risk of genotoxic effects on sperm cells cannot be completely excluded.

In the absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measures are recommended. Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients are recommended to use highly effective contraception during treatment and for total of 90 days after the last dose of MMF.

Use in Lactation

It is not known whether this medicine is excreted in human milk. Due to the potential for serious adverse reactions in nursing infants, MMF is contraindicated during breastfeeding (see section 4.3 Contraindications). Although the relevance to humans is unknown, studies in rats have shown MMF to be excreted in milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MMF may have a moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machinery if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with MMF (see section 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse event profile associated with the use of immunosuppressive medicines is often difficult to establish owing to the presence of underlying disease and the concurrent use of many other medications. The principal adverse reactions associated with the administration of MMF in combination with ciclosporin and steroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections, such as tuberculosis and atypical mycobacterial infection. Uncommon but serious life-threatening infections such as meningitis and infectious endocarditis have been reported.

The incidence of adverse events for MMF was determined in 3 randomised comparative double-blind trials in prevention of rejection in renal transplant patients. However, due to the lower overall reporting of events in the placebo-controlled prevention of rejection study, these data were not combined with the other two active-controlled prevention trials but are instead presented separately.

Patients in the double-blind studies of the prevention of renal allograft rejection were treated for up to a minimum of 1 year, with approximately 53% of the patients having been treated for more than 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the MMF 2 g or 3 g treatment groups are presented below, for the two active-controlled studies combined, and for the one placebo-controlled study.

Table 1: Adverse Events in Prevention of Renal Allograft Rejection

	Active – Controlled Studies			*Placebo – Controlled Study*		
	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n = 326)	**MMF 2 g/day (n = 336)**	**MMF 3 g/day (n = 330)**	**Placebo (n = 166)**	**MMF 2 g/day (n = 165)**	**MMF 3 g/day (n = 160)**
Digestive System						
Diarrhoea	12.6%	17.9%	23.3%	9.6%	9.1%	13.1%
Constipation	11.0	12.2	7.9	1.2	3.0	1.3
Dyspepsia	8.9	10.4	7.3	1.8	1.2	0.6
Oral Moniliasis	11.0	9.8	12.1	6.6	6.1	3.1
Nausea	10.7	9.5	12.1	2.4	2.4	4.4
Nausea And Vomiting	7.7	6.0	5.2	1.2	0.6	0
Vomiting	4.6	5.1	4.8	1.2	1.2	1.9
Oesophagitis	2.1	4.2	4.8	0.6	0	0
Gastritis	0.6	4.2	3.0	1.2	1.2	2.5
Flatulence	3.4	3.9	1.8	0	1.8	0
Liver Function Tests Abnormal	2.5	3.0	2.1	6.0	3.0	3.1
Gastrointestinal Moniliasis	1.8	3.0	2.4	0	1.8	1.3
Gastroenteritis	0.3	1.5	1.8	1.8	2.4	4.4
Infection	0.6	0.9	3.3	1.2	1.8	2.5
Body as a Whole						
Abdominal Pain	9.2	13.4	12.1	7.2	6.7	5.6
Sepsis	11.7	12.5	12.7	13.3	21.8	17.5
Infection	6.1	4.5	6.1	12.7	12.7	15.0
Fever	2.8	4.5	4.2	1.8	2.4	3.1
Headache	4.0	3.9	2.7	0.6	0	0
Pain	2.1	3.6	1.8	1.8	0.6	0.6
Flu Syndrome	0.6	0.9	0.6	2.4	3.6	5.0
Asthenia	1.8	1.8	3.0	0.6	0	0
Urogenital System						
Urinary Tract Infection	10.7	13.4	11.5	37.3	45.5	44.4
Pyelonephritis	0.3	0.3	0.3	3.0	3.6	1.9

Haemic and Lymphatic System						
Leucopenia	22.1	19.0	31.2	3.0	9.7	11.9
Thrombocytopenia	9.5	6.0	4.8	3.0	4.2	2.5
Anaemia	3.4	6.0	4.8	0.6	1.2	2.5
Leucocytosis	2.5	2.1	3.6	0	0	0.6
Respiratory System						
Infection	3.1	3.6	4.5	7.8	13.9	11.9
Pneumonia	1.2	2.1	1.5	10.8	3.6	10.6
Bronchitis	0.3	1.5	0.6	8.4	8.5	11.3
Pharyngitis	0.9	0.9	2.7	4.2	2.4	3.1
Metabolic and Nutritional Disorders						
Lactic Dehydrogenase Increased	4.9	5.1	5.2	0	0	0
Hypophosphataemia	4.3	5.4	5.2	0	0	0
SGPT Increased	2.8	3.9	3.0	1.2	1.2	1.9
Alkaline Phosphatase Increased	1.8	4.2	2.7	0.6	0	1.9
Hyperlipidaemia	3.1	3.3	3.0	0	0.6	0
SGOT Increased	1.5	2.7	3.3	0	0	0
Creatinine Increased	0.9	0.3	0.6	1.2	1.8	3.1

Patients in a double-blind study of the prevention of cardiac allograft rejection were treated for up to a minimum of 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the MMF 3 g or azathioprine treatment groups are presented below.

Table 2: Adverse Events in Prevention of Cardiac Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active - Controlled Cardiac Study	
	MMF 3 g/day (n = 289)	**Azathioprine 1.5-3.0 mg/kg/day (n = 289)**
Digestive System		
Nausea	21.8	17.6
Diarrhoea	14.2	11.8
Oral Moniliasis	11.4	11.8

Vomiting	9.7	11.4
Dyspepsia	7.3	5.5
Constipation	5.5	6.6
Flatulence	3.1	5.5
Gastritis	5.2	2.8
Nausea And Vomiting	3.5	3.1
Anorexia	3.8	2.4
Liver Damage	3.1	3.1
Liver Function Tests Abnormal	3.1	2.1
Haemic and Lymphatic System		
Leucopenia	26.0	36.3
Anaemia	6.2	7.6
Thrombocytopenia	3.5	6.6
Body as a Whole		
Sepsis	9.7	10.0
Headache	7.3	9.0
Abdominal Pain	7.6	7.3
Infection	8.7	5.9
Fever	1.0	3.1
Metabolic and Nutritional Disorders		
Bilirubinaemia	6.2	7.3
SGPT Increased	3.8	4.2
SGOT Increased	2.4	4.2
Alkaline Phosphatase Increased	2.4	3.8
Lactic Dehydrogenase Increased	2.8	3.5
Respiratory System		
Infection	2.4	4.2
Pneumonia	1.7	3.1
Nervous System		
Insomnia	3.1	2.1
Urogenital System		

Urinary Tract Infection	4.2	4.5

Patients in a double-blind study of the prevention of hepatic allograft rejection were followed for up to a minimum of 1 year. The adverse events reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the MMF 3 g or azathioprine treatment groups are presented below.

Table 3: Adverse Events in Prevention of Hepatic Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active - Controlled Hepatic Study	
	MMF 3 g/day (n = 277)	**Azathioprine 1-2 mg/kg/day (n = 287)**
Digestive System		
Diarrhoea	28.2	25.4
Nausea	26.7	19.9
Vomiting	11.9	12.2
Oral Moniliasis	9.4	9.8
Dyspepsia	6.5	10.1
Hepatitis	4.7	8.0
Anorexia	7.9	4.5
Constipation	5.4	4.5
Flatulence	5.4	3.1
Liver Function Tests Abnormal	4.0	3.1
Gastrointestinal moniliasis	2.5	4.2
Infection	3.2	2.8
Melaena	3.2	2.8
Haemic and Lymphatic System		
Leucopenia	42.2	35.2
Anaemia	12.6	19.9
Thrombocytopenia	14.4	16.0
Hypochromic Anaemia	6.1	4.2
Leucocytosis	4.3	4.9
Body as a Whole		
Sepsis	18.8	20.2
Abdominal Pain	15.9	11.5
Fever	8.7	9.4

Infection	7.9	9.4
Headache	7.6	7.3
Peritonitis	3.2	4.9
Abdomen Enlarged	4.0	3.5
Asthenia	2.2	3.1
Respiratory System		
Infection	4.0	6.6
Respiratory Moniliasis	4.3	5.6
Pneumonia	4.7	2.4
Nervous System		
Insomnia	5.1	4.5
Tremor	3.6	2.1
Urogenital System		
Urinary Tract Infection	7.6	9.4
Cardiovascular System		
Hypertension	6.5	2.8
Skin and Appendages		
Herpes Simplex	9.4	5.6
Herpes Zoster	4.0	4.9

The following adverse events, considered by the investigator to be possibly or probably related to drug treatment and not mentioned in any of the tables above or in text pertaining to infections or malignancy following, were reported with an incidence of less than 3% in one or more of the MMF 2 g or 3 g (renal) active-controlled cohorts (n = 336, n = 330), the MMF 2 g or 3 g (renal) placebo-controlled cohorts (n = 165, n = 160), less than 1.4% in the MMF 3 g (cardiac) active-controlled cohort (n = 289), or less than 1.4 % in the MMF 3 g (hepatic) active-controlled cohort study (n = 277).

Digestive System: colitis (sometimes caused by cytomegalovirus), ileus, duodenal ulcer, rectal disorder, stomach ulcer, duodenitis, gastrointestinal haemorrhage, mouth ulceration, dysphagia, peptic ulcer, cholecystitis, gastrointestinal disorder, ulcerative stomatitis, cheilitis, large intestine perforation, periodontal abscess, haemorrhagic gastritis, gum hyperplasia, stomatitis, eructation, haemorrhagic pancreatitis, intestinal necrosis, intestinal perforation, intestinal ulcer, gingivitis, glossitis, oesophageal ulcer, pancreatitis, apthous stomatitis, enteritis, faecal impaction, stomach atony, haematemesis, duodenal ulcer haemorrhage, proctitis, rectal haemorrhage, gastrointestinal carcinoma, faecal incontinence, pancreas disorder, stomach ulcer haemorrhage, cholangitis, hepatic failure, perforated peptic ulcer, ulcerative colitis.

Body as a Whole: back pain, ciclosporin level increased, chest pain, reaction unevaluable, accidental injury, abscess, lab test abnormal, cyst, neoplasm, chills, face oedema, malaise, substernal chest pain, carcinoma,

moniliasis, chills and fever, sarcoma, adenoma, granuloma, lack of drug effect, syncope, pelvis pain, pain, oedema, drug level increased, drug level decreased, injection site reaction, injection site inflammation, injection site hypersensitivity.

Urogenital System: dysuria, cystitis, haematuria, infection, oliguria, urinary frequency, pyuria, kidney abscess, abnormal kidney function, urethritis, urogenital carcinoma, kidney pain, nephritis, urethral pain, urinary urgency, urinary tract disorder, hydronephrosis, epididymitis, kidney tubular necrosis, urogenital occlusion, bladder neoplasm, urinary incontinence, vaginal moniliasis, kidney failure, urine abnormality.

Reproductive System: vaginal moniliasis, metrorrhagia, prostatic disorder, amenorrhoea, balanitis, cervix disorder, endometrial carcinoma, vaginal haemorrhage, impotence, breast pain, gynaecomastia, penis disorder.

Skin and Appendages: alopecia, fungal dermatitis, skin benign neoplasm, rash, acne, cutaneous moniliasis, pruritus, infection, urticaria, cellulitis, sweating, haemorrhage (skin and appendages), vesiculobullous rash, skin disorder, skin hypertrophy, skin ulcer, furunculosis, injection site inflammation, maculopapular rash, petechial rash, seborrhoea, skin carcinoma, skin discolouration.

Haemic and Lymphatic System: pancytopenia, polycythemia, thrombocythemia, agranulocytosis, lymphoma like reaction, decreased immunoglobulins, ecchymosis, thrombotic thrombocytopenic purpura, epistaxis, haemorrhage, petechia, abnormal WBC, blood dyscrasia, haemolytic anaemia, lymphadenopathy, hepatitis B serum antigen positive, reticuloendothelial hyperplasia, marrow hyperplasia, coagulation disorder, haemolysis.

Respiratory System: sinusitis, cough increased, dyspnoea, rhinitis, respiratory abscess, interstitial pneumonia, lung carcinoma, lung disorder, asthma, laryngismus, laryngitis, pneumothorax, hypoxia, atelectasis, lung oedema, lung fibrosis, pleural effusion, pleural disorder.

Metabolic and Nutritional Disorders: gamma glutamyl transpeptidase increased, hypercholesterolaemia, hypokalaemia, acidosis, increased creatinine, bilirubinaemia, peripheral oedema, increased amylase, healing abnormal, hypocalcaemia, hyperglycaemia, albuminuria, weight loss, BUN increased, dehydration, decreased gamma globulin, hypercalcaemia, hypervolaemia, hypoproteinaemia, uremia, hyperkalaemia, hyperchloraemia, enzymatic abnormality, hypomagnesaemia, increased creatine phosphokinase, hyperuricaemia, hyponatraemia, diabetes mellitus, gout, respiratory acidosis, oedema, hypoglycaemia, cachexia, hyperphosphataemia.

Liver and Biliary System: liver damage, cholestatic jaundice, cholelithiasis.

Cardiovascular System: pulmonary embolus, thrombosis, palpitation, angina pectoris, vasodilatation, arterial thrombosis, cerebrovascular accident, phlebitis, atrial fibrillation, supraventricular tachycardia, cyanosis, cerebral ischaemia, hypotension, peripheral gangrene, tachycardia, arrhythmia, heart arrest, occlusion, shock, gangrene, deep thrombophlebitis, myocardial infarct, cardiomegaly, ventricular extrasystoles, ventricular tachycardia, cerebral ischaemia, myocarditis, endocarditis, heart failure, pulmonary hypertension, cardiomyopathy, electrocardiogram abnormal, , pericardial effusion.

Central and Peripheral Nervous System: hypertonia, dizziness, anxiety, vocal cord paralysis, neuropathy, paraesthesia, convulsion, depression, confusion, amnesia, depersonalisation, encephalitis, psychosis, agitation, hallucinations, aphasia, delirium, encephalopathy, hyperaesthesia, nystagmus, speech disorder, thinking abnormal, vertigo, apathy, catatonic reaction, CNS neoplasia, delusions, hemiplegia, hostility, hypokinesia, opisthotonos, paranoid reaction, personality disorder, somnolence, hypesthesia, emotional lability, hyperkinesia, manic reaction.

Special Senses: otitis media, infection, conjunctivitis, eye haemorrhage, blepharitis, ear pain, visual disturbance, lacrimation disorder, corneal ulcer, deafness, diplopia, retinal disorder, taste loss, keratitis, retinitis, ear disorder, vestibular disorder, eye disorder, taste perversion, tinnitus, otitis externa, amblyopia, abnormal vision, eye pain, photophobia.

Musculo-Skeletal System: arthralgia, bone pain, leg cramps, myalgia, bone necrosis, joint disorder, myasthenia, myopathy, osteoporosis.

Endocrine: sialadenitis, hormone level altered, hypothyroidism.

Up to 0.5% (regardless of investigator assessment of causality) of patients receiving MMF 2 g for prevention of renal allograft rejection developed severe neutropenia (absolute neutrophil count (ANC) < 5 x 10^8/L). Up to 2.8% (regardless of investigator assessment of causality) of cardiac transplant patients receiving MMF 3 g and up to 3.6% (regardless of investigator assessment of causality) of patients receiving MMF 3 g in hepatic transplantation developed severe neutropenia.

Cytomegalovirus (CMV) tissue invasive disease was more common in renal transplant patients receiving MMF 3 g/day (8 - 12%) than in those receiving MMF 2 g/day (4 - 8%) or control therapy (2 - 6%) in the three controlled studies for prevention of renal allograft rejection (percentage incidences have been determined regardless of investigator assessment of causality). In the placebo-controlled renal study, there was an increased incidence of *Herpes simplex* and *Herpes zoster* infections in patients receiving MMF compared to placebo. In addition, the incidence of overall infection with Candida and CMV viraemia/syndrome were similar in the three treatment groups. The following tables show the incidence of select opportunistic infections in the prevention of rejection trials:

Table 4: Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

	Renal Studies			*Cardiac Study*		*Hepatic Study*	
	MMF 2 g/day	**MMF** 3 g/day	**Azathioprine** 1-2 mg•kg^{-1}•day^{-1} or 100-150 mg/day	**MMF** 3 g/day	**Azathioprine** 1.5-3 mg•kg^{-1}•day^{-1}	**MMF** 3 g/day	**Azathioprine** 1-2 mg•kg^{-1}•day^{-1}
	(n = 336)	**(n = 330)**	**(n = 326)**	**(n = 289)**	**(n = 289)**	**(n = 277)**	**(n = 287)**
	%	%	%	%	%	%	%
Herpes simplex	16.7	20.0	19.0	20.8	14.5	10.1	5.9
CMV							
Viraemia/ syndrome	13.4	12.4	13.8	12.1	10.0	14.1	12.2
Tissue invasive disease	8.3	11.5	6.1	11.4	8.7	5.8	8.0
Herpes zoster	6.0	7.6	5.8	10.7	5.9	4.3	4.9
Cutaneous disease	6.0	7.3	5.5	10.0	5.5	4.3	4.9
Candida	17.0	17.3	18.1	18.7	17.6	22.4	24.4
Mucocutaneous	15.5	16.4	15.3	18.0	17.3	18.4	17.4

The following other opportunistic infections occurred with an incidence of less than 4% in MMF patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease; Candida, urinary tract infection, fungemia/ disseminated disease, tissue invasive disease; Cryptococcosis; Aspergillus/Mucor; Pneumocystis carinii.

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal study, with a notably lower incidence of Herpes simplex and CMV tissue-invasive disease.

In the three controlled studies for prevention of rejection in renal transplantation, similar rates of fatal infections/sepsis (< 2%) have occurred in patients receiving MMF or control therapy in combination with other immunosuppressive agents. In the controlled cardiac transplant study, fatal infections occurred in 2.4% of patients receiving MMF 3 g compared to 4.5% of patients receiving azathioprine, both in combination with other immunosuppressive agents. In the controlled hepatic transplant study, fatal infection/sepsis occurred in 5.4% of patients receiving MMF 3 g compared to 7.3% receiving azathioprine, both in combination with other immunosuppressive agents.

As with other patients receiving immunosuppressive regimes involving combinations of drugs, patients receiving MMF as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. Within 3 years post-transplant, lymphoproliferative disease or lymphoma developed in patients receiving MMF in immunosuppressive regimes in 0.6% of patients receiving 2 g daily in the controlled studies of prevention of renal rejection compared to placebo (0%) and azathioprine groups (0.6%).

The incidence of malignancies among the 1 483 patients enrolled in controlled trials for the prevention of renal allograft rejection was low, and similar to the incidence reported in the literature for renal allograft recipients. There was a slight increase in the incidence of lymphoproliferative disease in the MMF treatment groups compared to the placebo and azathioprine groups. The following table summarises the incidence of malignancies observed in the prevention of rejection trials.

Table 5: Malignancies Observed in Prevention of Renal, Cardiac and Hepatic Rejection Trials

No. of patients (%) with one or more malignancies

(Regardless of Investigator Assessment of Causality)

	Renal Studies				**Cardiac Study**		**Hepatic Study**	
	Placebo	**Azathioprine** *1-2 mg/kg/day or 100-150 mg/day*	**MMF** *2 g/day*	**MMF** *3 g/day*	**Azathioprine** *1.5-3 mg/kg/day*	**MMF** *3 g/day*	**Azathioprine** 1-2 mg/kg/day	**MMF** *3 g/day*
	(n=166)	**(n=326)**	**(n=501)**	**(n=490)**	**(n=289)**	**(n=289)**	**(n=287)**	**(n=277)**
Lymphoma /lympho-proliferative disease	0	0.3	0.6	1.0	2.1	0.7	0	0.4
Non-melanoma skin carcinoma	0	2.4	4.0	1.6	2.8	4.2	2.1	2.2
Other malignancy	1.8	1.8	0.8	1.4	2.1	2.1	2.4	0.7

Three-year safety data in renal and cardiac transplant patients indicated that the overall incidence of malignancy was comparable between MMF and azathioprine groups. Hepatic transplant patients were followed for at least 1 year but less than 3 years.

Paediatric Adverse Events

The type and frequency of adverse drug reactions in a clinical study of 100 paediatric patients 3 months to 18 years of age given 600 mg/m^2 MMF orally twice daily were generally similar to those observed in adult patients given 1 g MMF twice daily with the exception that paediatric patients had a higher proportion of diarrhoea, anaemia, sepsis and leucopenia.

Post-Marketing Experience

Infections: uncommon: Serious life-threatening infections such as meningitis, protozoal infections and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infections.

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in MMF-treated patients. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function.

BK virus-associated nephropathy has been observed in patients treated with MMF. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

Neoplasm benign, malignant and unspecified (including cysts and polyps): Lymphoma, lymphoproliferative disorder.

Gastrointestinal: uncommon: pancreatitis, isolated cases of intestinal villous atrophy, colitis (sometimes caused by cytomegalovirus).

Congenital Disorders: congenital malformations have been reported post marketing in children of patients exposed to MMF in combination with other immunosuppressants during pregnancy (see section 4.6 Fertility, Pregnancy and Lactation).

Pregnancy, Puerperium and Perinatal Conditions: Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate mofetil have been reported (see section 4.6 Fertility, Pregnancy and Lactation).

Blood and Immune System: Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with MMF in combination with other immunosuppressive agents, hypersensitivity.

Respiratory, thoracic and mediastinal disorders: Bronchiectasis, interstitial lung disease, pulmonary fibrosis.

Vascular disorders: Lymphocele.

General disorders and administration site conditions: De novo purine synthesis inhibitors associated acute inflammatory syndrome is a newly described paradoxical pro-inflammatory reaction associated with mycophenolate and other purine synthesis inhibitors, characterised by fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers. Anecdotal literature reports showed rapid improvements following discontinuation of the drug.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Reports of overdoses with MMF have been received from clinical trials and during post-marketing experience. In many of these cases no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the drug.

Symptoms

It is expected that an overdose of MMF could possibly result in over-suppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4 Special Warnings and Precautions for Use). If neutropenia develops, dosing with MMF should be interrupted or the dose reduced (see section 4.4 Special Warnings and Precautions for Use).

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 μg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as colestyramine, can remove MPA by increasing excretion of the drug (see section 5.2 Pharmacokinetic Properties).

Treatment

Treatment of overdosage should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mycophenolic acid (MPA) is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) which inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Based on Chinese hamster inosine-5'-monophosphate dehydrogenase (IMPDH) in complex with inosine-5'-monophosphate (IMP) and mycophenolic acid (MPA), the mechanism by which MPA

inhibits the enzymic activity of IMPDH (human type II) appears to be related to the ability of MPA to structurally mimic both the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthos-5'-monophosphate, the committed step in the de novo guanosine nucleotide biosynthesis. Human type II and Chinese hamster IMPDH differ by six amino acids but have similar enzymatic characteristics. MPA has more potent cytostatic effects on lymphocytes than on other cells because T- and B-lymphocytes are dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilise salvage pathways. Depletion of guanosine nucleotides leads to the inhibition of glycosylation of adhesion molecules on lymphocytes, a process also considered an action of mycophenolate mofetil.

Mycophenolate mofetil (MMF) has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). MMF has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. MMF was used alone or in combination with other immunosuppressive agents in these studies.

In experimental animals, MMF has been demonstrated to prevent inflammatory responses that are immunologically mediated, and to delay tumour development and prolong survival in models of xenogeneic human to mouse and syngeneic murine tumours in vivo.

MMF, the 2-morpholinoethyl ester of MPA is rapidly absorbed following oral administration and hydrolysed to form free MPA, which is the active metabolite. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation.

Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes, showing the specificity of action of the drug. MPA also suppresses antibody formation by B-lymphocytes. By depletion of guanosine nucleotides, MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells. By this mechanism, MPA may inhibit recruitment of leucocytes into sites of inflammation and graft rejection.

MMF did not inhibit early events in the activation of human peripheral blood mononuclear cells such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Animal studies have shown that mortality in rats with Pneumocystis carinii pneumonia is higher during combined treatment with MMF and trimethoprim/sulfamethoxazole than with either drug alone. MMF did not interfere with the ability of trimethoprim/sulfamethoxazole to reduce the incidence of P. carinii cysts in surviving animals, and reduced the incidence of cysts when administered by itself.

Clinical Trials

1. Prevention of Acute Renal Rejection Episodes

The safety and efficacy of mycophenolate mofetil as adjunctive therapy for the prevention of organ rejection following allogeneic renal transplants were assessed in three randomised, double-blind, multicentre trials.

These studies compared two dose levels of MMF (1 g twice daily and 1.5 g twice daily) with azathioprine (2 studies) or placebo (1 study) when administered in combination with ciclosporin and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced biopsy-proven acute rejection or treatment failure (defined as early termination from the study for any reason without prior biopsy-proven rejection) within the first six months after transplantation. MMF, when administered with ATGAM® induction (one study) and with ciclosporin and corticosteroids (all three studies) was shown to be superior to the following three therapeutic regimens: (1) ATGAM® induction / azathioprine / ciclosporin / corticosteroids, (2) azathioprine / ciclosporin / corticosteroids, and (3) ciclosporin / corticosteroids. The superior efficacy of MMF as adjunctive therapy, when compared to azathioprine or placebo, was demonstrated by a reduction in the incidence of first biopsy-proven acute rejection episode or treatment failure within the first 6

months following transplantation. In addition, MMF reduced the incidence of first biopsy-proven acute rejection episodes within the first six months after transplantation.

In Table 6 table below, the percentages for first biopsy-proven rejection alone have not been adjusted for patients who terminated prematurely before experiencing a biopsy-proven rejection episode.

Table 6: Incidence of Biopsy Proven-Rejection or Treatment Failure

Induction, Azathioprine-Controlled	**Azathioprine**	**MMF**	**MMF**
(n = 499 patients)	**1-2 mg/kg/day**	**2 g/day**	**3 g/day**
	(n = 166 patients)	**(n = 167)**	**(n = 166)**
First biopsy-proven rejection episode or treatment failure	47.6 %	31.1 %	31.3 %
First biopsy-proven rejection episode alone	38.0 %	19.8 %	17.5 %
No Induction, Azathioprine-Controlled	**Azathioprine**	**MMF**	**MMF**
(n = 503 patients)	**100-150 mg/day**	**2 g/day**	**3 g/day**
	(n = 166)	**(n = 173)**	**(n = 164)**
First biopsy-proven rejection episode or treatment failure	50.0 %	38.2 %	34.8 %
First biopsy-proven rejection episode alone	35.5 %	19.7 %	15.9 %
No Induction, Placebo-Controlled	**Placebo**	**MMF**	**MMF**
(n = 491 patients)	**(n = 166)**	**2 g/day**	**3 g/day**
		(n = 165)	**(n = 160)**
First biopsy-proven rejection episode or treatment failure	56.0 %	30.3 %	38.8 %
First biopsy-proven rejection episode alone	46.4 %	17.0 %	13.8 %

In these three studies, the proportion of patients requiring antilymphocyte therapy for treatment of rejection during the first 6 months following transplantation was smaller among patients receiving MMF 2 g per day (5.5 to 10.3%) or MMF 3 g per day (3.1 to 5.4%) than among patients receiving azathioprine or placebo (15 to 21%).

Six- and twelve-month patient survival and graft survival was somewhat higher in the patients receiving MMF in comparison to either azathioprine or placebo. The cumulative proportions of patients who had died or lost their graft by 6 and 12 months post-transplant were as follows:

Table 7: Cumulative Incidence of Combined Graft Loss & Patient Death at 6 (12) Months

Study	**Control (Azathioprine or Placebo)**	**MMF 2 g/day**	**MMF 3 g/day**
Induction, Azathioprine-Controlled	10.4 % (12.2 %)	5.5 % (8.5 %)	8.5 % (11.5 %)
No Induction, Azathioprine-Controlled	11.7 % (13.6 %)	8.8 % (11.7 %)	6.7 % (11.0 %)
No Induction, Placebo-Controlled	10.2 % (11.5 %)	6.7 % (8.5 %)	8.8 % (10.0 %)

2. Treatment of Refractory Renal Rejection

The safety and efficacy of MMF as adjunctive therapy for the treatment of refractory organ rejection following allogeneic renal transplants was assessed in one randomised, open-label, multicentre trial. This study was designed to evaluate whether MMF at a dose of 1.5 g twice daily was superior to high dose IV steroids. In this

study, all patients continued to receive concomitant maintenance oral corticosteroids and ciclosporin. The control group received IV methylprednisolone (5 mg/kg/day for 5 days followed by an oral course with tapered doses of corticosteroids); the control patients also generally received azathioprine. A total of 150 patients were enrolled (73 assigned to receive IV steroids; 77 assigned to receive MMF). Patients enrolled in this study had recurrent or persistent allograft rejection following treatment with either Orthoclone OKT3®, ATGAM®, or antilymphocyte globulin for at least 7 days, the last day of which occurred within 28 days prior to entry into the study. In addition, patients showed renal biopsy findings consistent with acute rejection at study entry. Serum creatinine concentrations were 442 μmol/L or lower at study entry.

The primary efficacy endpoint was graft and patient survival at 6 months post-enrolment. MMF was shown to be clinically effective in this study as evidenced by a 45% reduction in the number of patients who died or lost their graft. By 6 months post-enrolment, 26% of the IV steroid group and 14.3% of the MMF group had died or experienced graft loss. Eighteen patients (25%) receiving high dose IV steroids and 9 patients (12%) receiving MMF lost their graft in the 6 months after enrolment. One patient (1.4%) receiving high dose IV steroids and 2 patients (2.6%) receiving MMF died in the 6 months after enrolment. Fewer patients receiving MMF (10.4%) required treatment with anti-lymphocyte preparations in the 6 months after enrolment, compared to those receiving high dose IV steroids (24.7%).

3. Prevention of Renal Rejection in Paediatrics

In a multicentre open-label, safety, tolerability and pharmacokinetic study of MMF oral suspension 600 mg/m^2 twice daily (up to 1 g twice daily) in combination with ciclosporin and corticosteroids in the US, Europe and Australia, 100 patients aged 3 months to 18 years of age received treatment for the prevention of renal allograft rejection. The primary efficacy endpoint was the proportion of patients experiencing an acute rejection episode in the first 6 months post-transplant. Results were analysed after 1 year and it was shown that MMF was well tolerated in paediatric patients (see section 4.8 Adverse Effects (Undesirable Effects)), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g twice daily. MMF capsules (see section 5.2 Pharmacokinetic Properties - Pharmacokinetics in Special Populations). The rate of biopsy-proven rejection was similar across the age groups (3 months to < 6 years, 6 to < 12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant were similar to the rates observed in adult renal transplant patients. Results out to 36 months post-transplant in children are currently under investigation.

4. Prevention of Cardiac Allograft Rejection

In a randomised, double-blind, parallel active-controlled multicentre study to compare the safety and efficacy of MMF 1.5 g twice daily with azathioprine 1.5 - 3 mg/kg/day, both in combination with ciclosporin and corticosteroids, 650 patients were randomised to the two arms. The primary endpoints investigated were (1) prevention of biopsy-proven acute rejection with haemodynamic compromise during the first six months following transplantation and (2) prevention of death or re-transplantation during the first year following cardiac transplantation. 72 patients were withdrawn prior to administration and without knowledge of the assigned therapy primarily because of perioperative adverse events, inability to take oral medication or death. Therefore, 289 patients received study medication in each arm.

Patients in the MMF arm had a lower incidence of death or re-transplantation, however this difference was within the protocol-defined range of equivalence, being a ± 10% mortality difference.

MMF and azathioprine did not differ significantly at 6 months in biopsy-proven acute rejection with haemodynamic compromise. Survival, acute rejection and composite endpoints are listed in the table below.

Table 8: survival, acute rejection and composite endpoints.

Parameter	Azathioprine n = 289 %	MMF n = 289 %
Survival Endpoint Death or retransplantation at 12 months post-transplant	11	6

Composite Failures at 12 months Death, ejection fraction < 30 %, coronary stenosis or myocardial infarction	14	8
Acute Rejection Endpoints Patients with Rejection at 6 months post-transplant 1. Including haemodynamic compromise (1) - with haemodynamic compromise - with severe haemodynamic compromise (cardiogenic) (2), (3) 2. By ISHLT Grade - grade 1A or greater - grade 2A or greater - grade 3A or greater 3. Including pulse treatment of rejection - biopsy proven rejection treated with pulse immunosuppressives (4) - biopsy proven or presumed rejection treated with pulse immunosuppressives (4) treated with OKT3 or ATG	 35 17 97 69 53 71 74 21	 32 11 95 65 45 64 66 15

(1) Haemodynamic compromise defined as one or more of the following:

Pulmonary capillary wedge pressure ≥ 20 mm or 25% increase

Cardiac index < 2.0 or 25% decrease

Ejection fraction ≤ 30%

Pulmonary artery saturation ≤ 60% or 25% decrease

Presence of S_3 gallop

Fractional shortening ≤ 20 % or 25% decrease

(2) Severe defined as requirement for inotropic support to manage any one of the clinical conditions listed above.

(3) Amongst patients who reached this acute rejection endpoint, no MMF-treated patients died during 12 months, versus 8 AZA recipients during 6 months and 12 AZA recipients who died during 12 months.

(4) Pulse immunosuppressives being corticosteroids and if required OKT3 by protocol-defined regimen (according to ISHLT biopsy grade and degree of haemodynamic compromise).

5. Prevention of Hepatic Allograft Rejection

The safety and efficacy of MMF was assessed in a randomised, double-blind, parallel, active-controlled, multicentre study in hepatic transplant patients. This study compared the use of MMF 1 g twice daily intravenously for up to 14 days followed by 1.5 g twice daily orally against azathioprine 1 - 2 mg/kg/day intravenously followed by 1 - 2 mg/kg/day orally, both in combination with ciclosporin and corticosteroids. 565 patients were randomised into the two arms, 278 patients in the MMF group and 287 patients in the azathioprine group.

The two primary endpoints investigated were (1) the proportion of patients who experienced, in the first 6 months post-transplantation, (a) one or more episodes of biopsy-proven and treated rejection or (b) death/re-transplantation, and (2) the proportion of patients with graft loss (death/re-transplantation) during the first 12 months post-transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/re-transplantation) for 1 year.

In the primary analyses MMF in combination with corticosteroids and ciclosporin was superior to azathioprine for prevention of acute rejection (p = 0.02) in the 6 months following transplant and equivalent to azathioprine for survival or graft loss in the 12 months following transplant.

Table 9: Two primary endpoints investigated

	Azathioprine n = 287 (%)	MMF n = 278 (%)	Difference [95% CI]
Biopsy-proven and treated rejection or death/retransplantation at 6 months	47.7	38.1	p = 0.02
Death or retransplantation at 12 months	14.6	14.0	0.5 (1) [-5.1, 6.0]

(1) Weighted point estimate of difference in proportions (azathioprine minus MMF). Met non-inferiority criterion of a lower bound > - 10%.

The superiority of MMF to azathioprine in the time to biopsy-proven and treated rejection or death/ re-transplantation in the 6 months following transplant approached statistical significance (log-rank p = 0.06). The time to death/re-transplantation in the 12 months following transplant was similar in the two treatment groups (log-rank p = 0.86).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, MMF undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, mycophenolic acid (MPA). MMF is not measurable systemically in plasma following oral administration. Modest concentrations of the parent drug are detected in plasma samples during intravenous infusion, but concentrations decline rapidly after the completion of the infusion. The mean extent of absorption of MPA during multiple dosing (as measured by the area under the plasma-concentration time curve, AUC) increases in a dose proportionate manner over a daily dose range of 1 g to 4 g in renal transplant patients.

The administration of a 1.5 g dose of MMF by the intravenous (IV) and oral routes to healthy volunteers resulted in similar plasma MPA and inactive glucuronide of MPA (MPAG) total AUC values. Recovery of MPAG in urine was the same for both routes indicating complete absorption of oral MMF. The mean bioavailability of orally administered MMF, based on MPA AUC, was 94% relative to IV administration.

The results of a single-dose bioequivalence study in 47 healthy volunteers indicated that the 500 mg tablet (x 2) was equivalent to the 250 mg capsule (x 4) with respect to the extent of absorption (AUC), but not the rate of absorption (C_{max}). The C_{max} for MPA of the tablet was 28% lower than that for the capsule.

Food had no effect on the extent of absorption (MPA AUC) of MMF when administered as 1.5 g twice daily doses to renal transplant patients. However, the C_{max} for MPA was decreased by 40% in the presence of food.

The pharmacokinetic profile of MPA in cardiac patients is similar to that in renal patients.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed approximately 6 to 12 hours post-dose. Co-administration of colestyramine (4 g three times daily) with MMF is associated with a reduction in the AUC of MPA of approximately 40% as a result of decreased enterohepatic recirculation. The majority of the difference in the AUC is in the terminal portion of the MPA plasma concentration time profile.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

Metabolism

MPA is metabolised principally by glucuronyl transferases (predominantly isoform UGT1A9) to form the pharmacologically inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).

Excretion

After oral administration, 93% of the dose was recovered from the urine and 6% from the faeces. The major metabolite of MMF excreted in urine is MPAG, which accounts for 87% of the oral MMF dose. Less than 1% of the dose was excreted as MPA in the urine. The following metabolites of the morpholino moiety are also recovered in the urine following oral administration of MMF: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Mean ± SD apparent half-life and plasma clearance of MPA are 17.9 ± 6.5 hours and 193 ± 48 mL/min respectively following oral administration.

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites inhibit renal organic anion transporters, with MPAG also being a substrate for OAT3.

Pharmacokinetics in Special Populations

Renal, Cardiac and Hepatic Transplant Patients

In renal, cardiac and hepatic transplant patients, mean steady state MPA AUC and C_{max} were up to 40% lower in the early post-transplant period (< 40 days post-transplant) compared to the late transplant period (3 - 6 months post-transplant).

In renal transplant patients, in the immediate post-transplant phase, mean steady state MPA AUC was 24% higher following 1 g twice daily intravenous MMF (over 2 hours) for 5 days compared with the same dose orally.

In cardiac transplant patients, administration of 1.5 g twice daily oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered the same dose.

In hepatic transplant patients, administration of 1 g twice daily intravenous MMF followed by 1.5 g twice daily oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered 1 g twice daily oral MMF.

Renal Impairment

In a single dose study (6 subjects per group), plasma MPA AUCs were up to 30% higher in subjects with mild to moderate renal impairment (GFR 25 - 80 mL/min/1.73m^2) and 75% higher in subjects with severe renal impairment (GFR < 25 mL/min/1.73m^2) than those subjects with normal renal function (GFR > 80 mL/min/1.73m^2). The mean increase in MPA AUC observed in subjects with severe renal impairment was comparable to the increase in MPA AUC seen when the dose of MMF is increased from a daily dose of 2 to 3 g (see section 4.2 Dose and Method of Administration). Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied. In addition, the single dose plasma AUC of MPAG was 3 to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Delayed Renal Graft Function Post-Transplant

In patients with delayed renal graft function post-transplant, mean AUC_{0-12} of MPA was comparable to that seen in post-transplant patients without delayed graft function. However, mean plasma AUC_{0-12} of MPAG was 2- to 3-fold higher than post-transplant patients without delayed graft function. Also, with repeated dosing, plasma concentrations of MPAG accumulated, whereas accumulation of MPA occurred to a lesser degree, if at all. High plasma concentrations of MPAG may displace MPA from its protein binding sites resulting in a transient increase in the plasma concentration of free MPA in patients with delayed graft function.

No dose adjustment is recommended although close monitoring is advised.

Haemodialysis

The pharmacokinetics of MMF during haemodialysis are not altered. Haemodialysis does not remove MPA or MPAG. At high concentrations (> 100 µg/mL), haemodialysis removes only small amounts of MPAG.

Hepatic Impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation was relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Elderly Patients

Pharmacokinetics in the elderly have not been formally evaluated.

Paediatric Patients

The pharmacokinetic parameters of the MPA and MPAG were evaluated in 55 paediatric renal transplant patients aged 1 to 18 years given 600 mg/m^2 MMF orally twice daily (up to a maximum of 1 g twice daily). This dose

achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g twice daily in the early and late post-transplant period. MPA AUC levels across age groups were similar in the early post-transplant period out to 9 months post-transplant. There is limited pharmacokinetic data available for children aged less than 2 years.

Plasma-Binding

MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges such as those normally seen in stable renal transplant patients; however, at higher concentrations of MPAG which are seen in patients with delayed graft function or with severe renal insufficiency, the bound fraction in vitro decreases to 62%.

In vitro studies to evaluate the effect of several agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 250 μg/mL with HSA) and MPAG (at greater than or equal to 460 μg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, naproxen, digoxin, ciclosporin, theophylline, tacrolimus, tolbutamide, propranolol, warfarin, and prednisone did not increase the free fraction of MPA. MPA at concentrations as high as 100 μg/mL had little effect on the binding of warfarin, digoxin or propranolol but decreased the binding of theophylline from 53% to 45% and decreased the binding of phenytoin from 90% to 87%.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

MMF did not induce point mutations (Ames assay) or primary DNA damage (yeast mitotic gene conversion assay) in the presence or absence of metabolic activation. MMF did not cause chromosomal damage in vivo at oral doses up to 3000 mg/kg (mouse micronucleus aberration assay) or in vitro with or without metabolic activation at concentrations up to 5 μg/mL (Chinese hamster ovary cell [CHO] chromosomal aberration assay). Chromosome aberrations were present without metabolic activation in an initial CHO cell assay, but only at concentrations (249 to 300 μg/mL) that cause excessive cytotoxicity.

Carcinogenicity

A 104-week oral carcinogenicity study in mice with MMF at daily doses of 25, 75 or 180 mg/kg showed an increase above control levels in the incidence of lymphosarcomas in females at the highest two dose levels and in males at the highest dose level (1.1 - 1.9 times the expected maximum clinical dose based on AUC values). The incidence of lymphosarcomas in all mice remained within the range of that observed historically in this strain of mice. In a 104-week oral carcinogenicity study in rats, MMF in daily doses up to 15 mg/kg (0.6 times the expected maximum clinical dose based on AUC values) was not tumourigenic.

The incidence of lymphoma/lymphoproliferative disease and other malignancies is also increased in patients on immunosuppressive agents, and this appears to be related to the intensity or duration of immunosuppression rather than any specific immunosuppressant agent (see section 4.4 Special Warnings and Precautions for Use).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CEPTOLATE is available as a caramel/lavender capsule containing 250 mg of mycophyenolate mofetil with the following excipients:

- microcrystalline cellulose
- pregelatinized maize starch
- silicon dioxide
- magnesium stearate
- sodium lauryl sulfate
- croscarmellose sodium

Empty Hard Gelatin Capsule Size 1 Lavender Op/Caramel OP G1HCSA00612 (Proprietary Ingredient No: 106636) contain:

- gelatin
- sodium lauryl sulfate
- sorbitan monolaurate
- shellac and
- ammonium hydroxide

The dyes in the capsule shell are:

- indigo carmine (CI No. 73012)
- iron oxide red (CI No.77491)
- Titanium dioxide (CI No. 77492)
- iron oxide yellow (CI No. 77492), and
- iron oxide black (CI No. 77499).

The printed ink on the capsule is OPACODE monogramming ink S-1-17822 Black (Proprietary Ingredient No. 12390) and OPACODE monogramming ink S-1-17823 Black (Proprietary Ingredient No. 12108).

CEPTOLATE is also available as a light pink-coloured film-coated tablet containing 500 mg of mycophenolate mofetil with the following excipients:

- microcrystalline cellulose
- pregelatinised maize starch
- povidone
- silicon dioxide
- magnesium stearate
- sodium lauryl sulfate
- croscarmellose sodium and
- OPADRY II Complete Film Coating System 85F94410 Pink (Proprietary Ingredient No. 106325).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC and protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

CEPTOLATE (mycophenolate mofetil) 250 mg	Capsules Available in PVC/Aclar/PVC/Al blister packs of 50, 100 and 300.
CEPTOLATE (mycophenolate mofetil) 500 mg	Tablets Available in PVC/Aclar/PVC/Al, PVC-Aclar / Al, or PVC/PE/PVdC/Al blister packs of 50 and 150.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 165766 – CEPTOLATE mycophenolate mofetil 250mg capsule blister pack

AUST R 163308 – CEPTOLATE mycophenolate mofetil 500 mg tablet blister pack

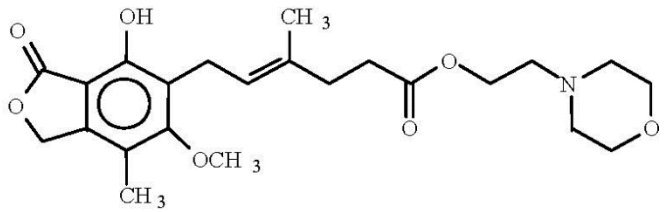
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

As MMF has demonstrated teratogenic effects (see section 4.4 Special Warnings and Precautions for Use and section 4.6 Fertility, Pregnancy and Lactation), MMF tablets and capsules should not be crushed or opened. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in MMF tablets and capsules. If contact occurs, wash thoroughly with soap and water. Should the eyes be affected, rinse eyes with plain water.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



2-Morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate.

Molecular formula: $C_{23}H_{31}NO_7$

Molecular weight: 433.50

Mycophenolate mofetil (MMF) is a white to off-white crystalline powder. It is freely soluble in dimethyl sulfoxide, tetrahydrofuran, acetone, acetonitrile, dichloromethane, and ethyl acetate; soluble in methanol and propylene carbonate; sparingly soluble in anhydrous ethanol; slightly soluble in 2-propanol, diethyl ether, and very slightly soluble in hexane. It is practically insoluble in water (43 μg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6).

CAS Number

128794-94-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

23/09/2001

10 DATE OF REVISION

25/05/2023

Summary Table of Changes

Section Changed	Summary of New Information
6.5	Addition of packaging materials for tablets. Update existing packaging of tablets and capsules to comply with ARTGs

CEPTOLATE_pi\May23/00