AUSTRALIAN PRODUCT INFORMATION – MYCOPHENOLATE APOTEX (MYCOPHENOLATE MOFETIL)

1 NAME OF THE MEDICINE

Mycophenolate mofetil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg mycophenolate mofetil

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Purple colored, capsule shaped, biconvex, film coated tablets debossed 'AHI' on one side and '500' on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants.

Prophylaxis of organ rejection in paediatric patients (with a body surface area >1.5 m^2) receiving allogeneic renal transplants.

4.2 DOSE AND METHOD OF ADMINISTRATION

The initial dose of mycophenolate 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.

Adults

Renal Transplantation

The recommended dose in renal transplant patients is 1 g administered orally.

Cardiac Transplantation

The recommended dose in cardiac transplant patients is 1.5 g administrated orally.

Hepatic Transplantation

The recommended dose in hepatic transplant patients is 1 g administrated intravenously twice daily (2 g daily dose) followed by 1.5 g administered orally twice daily (3 g daily dose).

Other Transplants

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

Paediatrics (6 to 18 years)

Mycophenolate is not suitable for paediatric patients whose body surface area is <1.50 m^2. Patients with a body surface area >1.5 m^2 may be dosed with mycophenolate at a dose of 1 g twice daily (2 g daily dose).

Mycophenolate may be administered in combination with cyclosporin 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 mycophenolate should be interrupted and the patient carefully observed (refer to 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/minute/1.73m^2) outside of the immediate post-transplant period, doses of mycophenolate 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 postoperatively.

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.

As mycophenolate mofetil has demonstrated teratogenic effects in rat and rabbit studies, the tablets should not be crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder. If contact occurs, wash thoroughly with soap and water, should the eyes be affected, rinse eyes with plain water.

4.3 CONTRAINDICATIONS

Allergic reactions to mycophenolate mofetil has been observed; therefore, this medicine is contraindicated in patients with hypersensitivity to mycophenolate mofetil or to mycophenolic acid.

Mycophenolate mofetil is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Section 4.6 Use in Pregnancy).

Mycophenolate mofetil is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Section 4.6 Use in Pregnancy).

Mycophenolate mofetil is contraindicated in women who are breastfeeding (see Section 4.6 Use in 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 mycophenolate. Mycophenolate mofetil is contraindicated during pregnancy and during breastfeeding (see Section 4.6 Use in Pregnancy and Use in Lactation).

As with other patients receiving immunosuppressive regimes involving combinations of medicines, patients receiving mycophenolate mofetil as part of an immunosuppressive regimen 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 mycophenolate mofetil 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.

Patients receiving mycophenolate mofetil 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 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 mycophenolate mofetil 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 mycophenolate mofetil-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 reporting neurological symptoms, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consult 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 at risk.

BK virus- associated neuropathy has been observed during the use of mycophenolate mofetil 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. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus –associated nephropathy.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil 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 mycophenolate mofetil therapy. In transplant patients however, reduced immunosuppression may place with graft at risk.

0.5% of patients receiving mycophenolate mofetil 2 g for prevention of rejection in renal transplantation, 2.8% of patients receiving mycophenolate mofetil 3 g in cardiac transplantation and 3.6% of patients receiving mycophenolate mofetil 3 g in hepatic transplantation, developed severe neutropenia (absolute neutrophil count [ANC] < $5x10^8$/L). 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) mycophenolate mofetil dosing should be interrupted or the dose reduced. Appropriate diagnostic testing should be performed and the patient managed accordingly.

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

Since mycophenolate mofetil 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 syndromes.

Gastrointestinal

Gastrointestinal tract bleeding (requiring hospitalisation) has been observed in approximately 1.4% of patients treated with mycophenolate mofetil 2 g in renal transplantation, 2.8% of patients receiving 3 g in cardiac transplantation and in 5.4% of patients receiving mycophenolate mofetil 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). It should be noted that patients with active peptic ulcer disease were excluded from enrolment in studies with mycophenolate mofetil. As mycophenolate mofetil 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 postmarketing surveillance, mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.

Use in Patients with Severe Chronic Renal Impairment

Patients with severe chronic renal impairment (GFR < 25 mL/minute/1.73m^2) who have received single doses of mycophenolate mofetil showed increased plasma AUCs of mycophenolic acid and glucuronide of mycophenolic acid 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 mycophenolate mofetil greater than 1g bd should be avoided (refer to Section 4.2 Dosage and Method of Administration and Section 5.2 Pharmacokinetic Properties).

In patients with delayed graft function post-transplant, mean mycophenolic acid $AUC_{(0-12)}$ was comparable, but MPAG $AUC_{(0-12)}$ was two to three 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 graft 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 mycophenolate mofetil than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed.

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

Laboratory monitoring

Patients on mycophenolate mofetil 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 mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to mycophenolate mofetil, concomitant medications, viral infections or some combination of these causes. If neutropenia (absolute neutrophil count < 1.3 x 10^3/µL), dosing with mycophenolate mofetil should be interrupted or the dose reduced and the patient should be carefully observed.

Use in the elderly

Elderly patients may be at an increased risk of certain infections (including cytomegalovirus (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. Elderly patients receiving mycophenolate mofetil as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including CMV tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals. Pharmacokinetic behaviour of mycophenolate mofetil in the elderly has not been formally evaluated.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug interaction studies with mycophenolate mofetil have been conducted with aciclovir, antacids, cholestyramine, cyclosporin A, ganciclovir, oral contraceptives, proton pump inhibitors, 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.

Azathioprine: It is recommended that mycophenolate mofetil 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.

Aciclovir: Following single dose administration of mycophenolate mofetil (1 g) and aciclovir (800 mg) to normal healthy subjects, higher glucuronide of mycophenolic acid (8.6%) and aciclovir (17.4%) plasma AUCs were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of each drug alone. As mycophenolate mofetil plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for the mycophenolate mofetil and acyclovir or the 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 mycophenolate mofetil (2 g) was decreased when aluminium/magnesium hydroxide antacids were administered concomitantly to rheumatoid arthritis patients. The C_{max} and 24 hour AUC values for mycophenolic acid were 33% and 17% lower, respectively than when mycophenolate mofetil was administered alone under fasting conditions.

Cholestyramine: Following single dose administration of mycophenolate mofetil 1.5 g in normal healthy subjects pretreated with cholestyramine three times daily 4 g for four days, there was a mean 40% reduction in the AUC of mycophenolic acid (see Section 5.2 Pharmacokinetic Properties). In view of the significant reduction in the AUC of mycophenolic acid by cholestyramine, caution should be used with the concomitant use of mycophenolate mofetil and any drug which interferes with enterohepatic circulation because of the potential to reduce the efficacy of mycophenolate mofetil.

Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) mycophenolic acid 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 mycophenolic acid exposure, therefore, clinical relevance of these observations is unclear.

Cyclosporin A: Cyclosporin A (CsA) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of mycophenolate mofetil 1.0 g bd in stable renal transplant patients. The mean (±SD) dose normalised $AUC_{(0\text{-}12\ hours)}$ of mycophenolic acid after 14 days and 3 months of multiple doses of mycophenolate mofetil and cyclosporin in 17 renal transplant patients were 43 ± 11 and 56 ± 31µg, hour.mL, respectively.

Sirolimus: A study in 36 renal transplant patients demonstrated that concomitant administration of mycophenolate mofetil (1 g bd) and sirolimus resulted in the mean (± SD) AUC(0-12 hours) of mycophenolic acid after 14 days and 3 months were 81 ± 36 and 71 ± 26µg. hour/mL 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 mycophenolate mofetil were withdrawn with symptoms consistent with mycophenolic acid or sirolimus toxicity.

Monitoring of mycophenolic acid 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 mycophenolate mofetil (1.5 g) and intravenous ganciclovir (5 mg/kg). However, as glucuronide of mycophenolic acid (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 mycophenolate mofetil and ganciclovir or its prodrugs (e.g. valganciclovir) are co administered, patients should be carefully monitored. However with mycophenolic acid no substantial alteration of MPA pharmacokinetics is anticipated and dose adjustment of mycophenolate mofetil is not required.

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

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: The pharmacokinetics of oral contraceptives were unaffected by co administration of mycophenolate mofetil. A study of co-administration of mycophenolate mofetil (1 g bd) and combined oral contraceptives containing ethinyloestradiol (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 three menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on serum levels of progesterone, LH and FSH, thus indicating no influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives (see Section 4.4 Special Warnings and Precautions for Use and Section 4.6 Use in Pregnancy).

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

has not been established, PPIs should be used with caution when co-administered to transplant patients treated with mycophenolate mofetil.

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

Tacrolimus: The AUC and C_{max} of mycophenolic acid, the active metabolite of mycophenolate mofetil, were not significantly affected by coadministration with tacrolimus, in stable hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5g bd) were administered to patients taking tacrolimus.

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

Trimethoprim/ Sulfamethoxazole: Following single dose administration of mycophenolate mofetil (1.5 g) to healthy male volunteers pretreated for ten days with trimethoprim 160 mg/ sulfamethoxazole 800 mg, no effect on the bioavailability of mycophenolic acid was observed.

Norfloxacin/ Metronidazole: The combination of norfloxacin and metronidazole reduced the MPA AUC following a single dose of mycophenolate mofetil.

Sevelamer and Other Calcium Free Phosphate Binders: Concomitant administration of sevelamer and mycophenolate mofetil in adults and paediatric patients decreased the C_{max} and $AUC_{(0\text{-}12)}$ of mycophenolic acid by 30% and 25%, respectively. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer. This data suggest that sevelamer and other calcium free phosphate binders should preferentially be given two hours after mycophenolate mofetil intake to minimise impact on the absorption of mycophenolic acid.

Other Interactions**:** The measured value for renal clearance of glucuronide of mycophenolic acid 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 mycophenolate mofetil in monkeys raises the plasma AUC of glucuronide of mycophenolic acid by threefold. Thus, other medicines known to undergo renal tubular secretion may compete with glucuronide of mycophenolic acid and thereby raise plasma concentrations of glucuronide of mycophenolic acid or the other drug undergoing tubular secretion.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day (0.8 times the expected maximum clinical dose based on AUC values). In a female fertility and reproduction study conducted in rats dosed orally at up to 4.5 mg/kg/day (0.1 times the maximum clinical dose based on AUC values), the 4.5 mg/kg/day dose caused malformations (principally of the head and eyes) in the first generation (F1) offspring in the absence of maternal toxicity. No effects on fertility were present in the treated females (P1 females), or in the subsequently mated first generation offspring (P2 females or P2 males).

Use in pregnancy (Category D)

Mycophenolate mofetil is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods (see Section 4.3 Contraindications).

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

Prior to starting therapy with mycophenolate mofetil, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25mIU/mL. The second test should be performed 8-10 days after the first one and immediately before starting mycophenolate mofetil. 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.

Due to the mutagenic and teratogenic potential of mycophenolate mofetil, women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning mycophenolate mofetil therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception. 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 mycophenolate mofetil.

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).

In the medical literature, malformations in children from mycophenolate mofetil exposed pregnancies have been reported in 23% to 27% of live births. 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.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate mofetil exposure, compared to a reported rate between 12% and 33% in solid organ transplant patients treated with other immunosuppressants.

In teratology studies, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (0.2 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 no effect levels for teratologic changes in rats and rabbits were 2 and 30 mg/kg/day, respectively.

Australian Categorization Definition of Category D
Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Use in lactation

Mycophenolate mofetil is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Section 4.3 Contraindications).

Studies in rats have shown mycophenolate mofetil to be excreted in milk. It is not known whether this medicine is excreted in human milk.

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). Data are insufficient to establish safety and efficacy in children below the age of 2 years.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

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 mycophenolate mofetil in combination with cyclosporin 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 mycophenolate mofetil was determined in three 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 one year, with approximately 53% of the patients having been treated for more than one 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 mycophenolate mofetil 2 or 3 g treatment groups, are presented in **Table 1**, 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 studies*		
	Azathio-prine 1-2 mg/kg/day or 100-150 mg/day (n = 326) %	**Mycophen-olate mofetil 2 g/day (n = 336) %**	**Mycophen-olate mofetil 3 g/day (n = 330) %**	**Placebo (n = 166) %**	**Mycophen-olate mofetil 2 g/day (n = 165) %**	**Mycophen-olate mofetil 3 g/day (n = 160) %**
Gastrointestinal						
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
Genitourinary/ 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
Haematological /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
Pharingitis	0.9	0.9	2.7	4.2	2.4	3.1
Metabolic/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
ALP 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 one 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 mycophenolate mofetil 3 g or azathioprine treatment groups are presented in **Table 2**.

Table 2 Adverse events in prevention of cardiac allograft rejection with an incidence of ≥ 3% in either treatment arm

	Active Controlled Cardiac study	
	Mycophenolate mofetil 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 treated for up to a minimum of one 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 mycophenolate mofetil 3 g or azathioprine treatment groups are presented in **Table 3.**

Table 3 Adverse events in prevention of hepatic allograft rejection with an incidence of ≥ 3% in either treatment arm

	Active Controlled Hepatic study	
	Mycophenolate mofetil 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
Gastointestinal 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, were reported with an incidence of less than 3% in one or more of the mycophenolate mofetil 2 g or 3 g (renal) active controlled cohorts (n = 336, n = 330), the mycophenolate mofetil 2 g or 3 g (renal) placebo-controlled cohorts (n = 165, n = 160), less than 1.4% in the mycophenolate mofetil 3 g (cardiac) active controlled cohort (n = 289), or less than 1.4 % in the mycophenolate mofetil 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, aphthous 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, cyclosporin 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, benign skin 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, polycythaemia, thrombocythaemia, agranulocytosis, lymphoma-like reaction, decreased immunoglobulins, ecchymosis, thrombotic thrombocytopenic purpura, epistaxis, haemorrhage, petechiae, 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, heart arrest, 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, hypaesthesia, 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 mycophenolate mofetil 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 mycophenolate mofetil 3 g and up to 3.6% (regardless of investigator assessment of causality) of patients receiving mycophenolate mofetil 3 g in hepatic transplantation developed severe neutropenia.

Cytomegalovirus (CMV) tissue invasive disease was more common in renal transplant patients receiving mycophenolate mofetil 3 g/day (8 - 12%) than in those receiving mycophenolate mofetil 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 mycophenolate mofetil compared to placebo. In addition, the incidence of overall infection with Candida and CMV viraemia/syndrome were similar in the three treatment groups.

Table 4 shows 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	
	Myco-phenolate mofetil 2 g/day (n = 336) %	**Myco-phenolate mofetil 3 g/day (n = 330) %**	**Azathio-prine 1-2 mg/kg/day or 100-150 mg/day (n = 326) %**	**Myco-phenolate mofetil 3 g/day (n = 289) %**	**Azathio-prine 1.5-3 mg/kg/day (n = 289) %**	**Myco-phenolate mofetil 3 g/day (n = 277) %**	**Azathio-prine 1-2 mg/kg/day (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 mycophenolate mofetil 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 mycophenolate mofetil or control therapy in combination with other immunosuppressive agents. In the controlled cardiac transplant study, fatal infections occurred in 2.4% of patients receiving mycophenolate mofetil 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 mycophenolate mofetil 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 mycophenolate mofetil as part of an immunosuppressive regimen are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. Within three years post transplant, lymphoproliferative disease or lymphoma developed in patients receiving mycophenolate mofetil in immunosuppressive regimens 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 mycophenolate mofetil treatment groups compared to the placebo and azathioprine groups. **Table 5** 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 (n = 166)	**Azathio-prine** 1-2 mg/kg/day or 100-150 mg/day (n = 326)	**Myco-pheno-late mofetil** 2 g/day (n = 501)	**Myco-pheno-late mofetil** 3 g/day (n = 490)	**Azathio-prine** 1.5-3 mg/kg/day (n = 289)	**Myco-pheno-late mofetil** 3 g/day (n = 289)	**Azathio-prine** 1-2 mg/kg/day (n = 287)	**Myco-pheno-late mofetil** 3 g/day (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	0	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 mycophenolate mofetil and azathioprine groups. Hepatic transplant patients were followed for at least one year but less than three 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 mycophenolate mofetil 600 mg/m^2 orally twice daily were generally similar to those observed in adult patients given mycophenolate mofetil 1 g 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 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 mycophenolate mofetil 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 mycophenolate mofetil. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

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 mycophenolate mofetil in combination with other immunosuppressants during pregnancy (see Section 4.6 Use in Pregnancy).

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 Use in Pregnancy).

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

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Reports of overdoses with mycophenolate mofetil 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.

It is expected that an overdose of mycophenolate mofetil 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 mycophenolate should be interrupted or the dose reduced (see Section 4.4 Special Warnings and Precautions for Use).

Treatment

Mycophenolic acid cannot be removed by haemodialysis. However, at high glucuronide of mycophenolic acid plasma concentrations (> 100 µg /ml), small amounts of glucuronide of mycophenolic acid are removed. Bile acid sequestrants, such as cholestyramine, can remove mycophenolic acid by increasing excretion of the drug (see Section 5.2 Pharmacokinetic Properties).

Treatment of overdosage should consist of general supportive measures.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (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 dehydrongenase (IMPDH) in complex with inosine-5'-monophosphate (IMP) and mycophenolic acid (MPA), the mechanism by which mycophenolic acid (MPA) inhibits the enzymatic activity of IMPDH (human type II) appears to be related to the ability of mycophenolic acid (MPA) to structurally mimic both the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of inosine-5'-monophosphate (IMP) to xanthos-5'-monophosphate, the committed step in the *de novo* guanosine nucleotide biosynthesis. Human type II and Chinese hamster inosine-5'-monophosphate dehydrongenase (IMPDH) differ by six amino acids but have similar enzymatic characteristics. Mycophenolic acid (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 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). Mycophenolate mofetil 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. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies.

In experimental animals, mycophenolate mofetil 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*.

Mycophenolate mofetil, the 2-morpholinoethyl ester of mycophenolic acid (MPA) is rapidly absorbed following oral administration and hydrolysed to form free MPA, which is the active metabolite. Mycophenolic acid (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 mycophenolic acid (MPA) on lymphocytes, showing the specificity of action of the drug. Mycophenolic acid (MPA) also suppresses antibody formation by B lymphocytes. By depletion of guanosine nucleotides, mycophenolic acid (MPA) prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells. By this mechanism, mycophenolic acid (MPA) may inhibit recruitment of leucocytes into sites of inflammation and graft rejection.

Mycophenolate mofetil 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 mycophenolate mofetil and trimethoprim/ sulfamethoxazole than with either drug alone. Mycophenolate mofetil 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 mycophenolate mofetil (1 g twice daily (bd) and 1.5 g bd) with azathioprine (two studies) or placebo (one study) when administered in combination with cyclosporin 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. Mycophenolate mofetil, when administered with ATGAM® induction (one study) and with cyclosporin and corticosteroids (all three studies) was shown to be superior to the following three therapeutic regimens: (1) ATGAM® induction / azathioprine / cyclosporin / corticosteroids; (2) azathioprine / cyclosporin / corticosteroids; (3) cyclosporin / corticosteroids. The superior efficacy of mycophenolate mofetil 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, mycophenolate mofetil reduced the incidence of first biopsy-proven acute rejection episodes within the first 6 months after transplantation.

In Table 6, 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 study Azathioprine-Controlled (n = 499 patients)	**Azathioprine 1-2 mg/kg/day (n = 166 patients)**	**Mycophenolate mofetil 2 g/day (n = 167)**	**Mycophenolate mofetil 3 g/day (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 (n = 503 patients)	**Azathioprine 100-150 mg/day (n = 166 patients)**	**Mycophenolate mofetil 2 g/day (n = 173)**	**Mycophenolate mofetil 3 g/day (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 (n = 491 patients)	Placebo (n = 166 patients)	Mycophenolate mofetil 2 g/day (n = 165)	Mycophenolate mofetil 3 g/day (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 six months following transplantation was smaller among patients receiving mycophenolate mofetil 2 g per day (5.5 to 10.3%) or mycophenolate mofetil 3 g per day (3.1 to 5.4%) than among patients receiving azathioprine or placebo (15 to 21%).

6 and 12 month patient survival and graft survival was somewhat higher in the patients receiving mycophenolate mofetil 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 are shown in **Table 7**.

Table 7 Cumulative incidence of combined graft loss and patient death at 6 (12) months

Study	Control (Azathioprine or Placebo)	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 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 mycophenolate mofetil 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 mycophenolate mofetil at a dose of 1.5 g bd was superior to high dose intravenous steroids. In this study, all patients continued to receive concomitant maintenance oral corticosteroids and cyclosporin. The control group received intravenous methylprednisolone (5 mg/kg/day for five 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 intravenous steroids; 77 assigned to receive mycophenolate mofetil). Patients enrolled in this study had recurrent or persistent allograft rejection following treatment with either Orthoclone OKT3®, ATGAM®, or antilymphocyte globulin for at least seven 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 six months post- enrolment. Mycophenolate mofetil 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 intravenous steroid group and 14.3% of the mycophenolate mofetil

group had died or experienced graft loss. 18 patients (25%) receiving high dose intravenous steroids and nine patients (12%) receiving mycophenolate mofetil lost their graft in the 6 months after enrolment. One patient (1.4%) receiving high dose intravenous steroids and 2 patients (2.6%) receiving mycophenolate mofetil died in the six months after enrolment. Fewer patients receiving mycophenolate mofetil (10.4%) required treatment with anti-lymphocyte preparations in the six months after enrolment, compared to those receiving high dose intravenous steroids (24.7%).

3. Prevention of Cardiac Allograft Rejection

In a randomised, double blind, parallel active controlled multicentre study to compare the safety and efficacy of mycophenolate mofetil 1.5 g bd with azathioprine 1.5 - 3 mg/kg/day, both in combination with cyclosporin 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 retransplantation 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 mycophenolate mofetil arm had a lower incidence of death or retransplantation, however this difference was within the protocol defined range of equivalence, being a ± 10% mortality difference.

Mycophenolate mofetil and azathioprine did not differ significantly at six months in biopsy proven acute rejection with haemodynamic compromise. Survival, acute rejection and composite endpoints are listed in **Table 8.**

Table 8 Incidence (%) of survival, acute rejection and composite endpoints in clinical trial investigating the efficacy and safety of mycophenolate mofetil versus azathioprine in preventing cardiac allograft rejection

Parameter	Azathioprine n = 289 %	Mycophenolate mofetil 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		
- with haemodynamic compromise [1]	35	32
- with severe haemodynamic compromise (cardiogenic) [2, 3]	17	11
By ISHLT Grade		
- grade 1A or greater	97	95
- grade 2A or greater	69	65
- grade 3A or greater	53	45
Including pulse treatment of rejection		
- biopsy proven rejection		
Treated with pulse immunosuppressives(4)	71	64
- biopsy proven or presumed rejection		
Treated with pulse immunosuppressives(4)	74	66
Treated with OKT3® or ATG	21	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 S3 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 mycophenolate mofetil-treated patients died during 12 months, versus 8 azathioprine recipients during 6 months and 12 azathioprine 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).*

4. Prevention of Hepatic Allograft Rejection

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

The two primary endpoints investigated were (1) the proportion of patients who experienced, in the first six months post-transplantation, (a) one or more episodes of biopsy proven and treated rejection or (b) death/retransplantation, and (2) the proportion of patients with graft loss (death/retransplantation) 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/retransplantation) for one year.

In the primary analyses mycophenolate mofetil in combination with corticosteroids and cyclosporin 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. See table 9.

Table 9

	Azathioprine n =287 (%)	**Mycophenolate mofetil 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* mycophenolate mofetil*). Met non inferiority criterion of a lower bound > - 10%.*

The superiority of mycophenolate mofetil to azathioprine in the time to biopsy-proven and treated rejection or death/retransplantation in the six months following transplant approached statistical significance (log rank p=0.06). The time to death/retransplantation 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 and intravenous administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, mycophenolic acid. Mycophenolate mofetil is not measurable systemically in plasma following oral administration. The mean extent of absorption of mycophenolic acid 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 to 4 g in renal transplant patients.

The administration of mycophenolate mofetil 1.5 g by the oral routes to healthy volunteers resulted in similar plasma mycophenolic acid and inactive glucuronide of mycophenolic acid total AUC values. Recovery of mycophenolic acid in urine was the same for both routes indicating complete absorption of oral mycophenolate mofetil. The mean bioavailability of orally administered mycophenolate mofetil, based on mycophenolic acid AUC, was 94%.

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

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

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma mycophenolic acid concentration are usually observed approximately 6 to 12 hours post-dose. CoA administration of cholestyramine (4 g three times daily) with mycophenolate mofetil is associated with a reduction in the AUC of mycophenolic acid 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 mycophenolic acid plasma concentration time profile.

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

Metabolism

Mycophenolic acid is metabolised principally by glucuronyl transferases to form the pharmacologically inactive phenolic glucuronide of mycophenolic acid. *In vivo*, glucuronide of mycophenolic acid, is converted to free mycophenolic acid via enterohepatic recirculation.

Excretion

After oral administration, 93% of the dose was recovered from the urine and 6% from the faeces. The major metabolite of mycophenolate mofetil excreted in urine is glucuronide of mycophenolic acid, which accounts for 87% of the oral mycophenolate mofetil dose. Less than 1% of the dose was excreted as mycophenolic acid in the urine. The following metabolites of the morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil: *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 mycophenolic acid are 17.9 ± 6.5 hours and 193 ± 48 mL/minute respectively following oral administration.

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 (three to six months post-transplant).

In renal transplant patients, in the immediate post-transplant phase, mean steady state (MPA AUC) was 24% higher following mycophenolate mofetil 1 g bd intravenous (over two hours) for five days compared with the same dose orally.

In cardiac transplant patients, administration of mycophenolate mofetil 1.5 g bd oral 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 mycophenolate mofetil 1 g bd intravenous followed by 1.5 g bd oral mycophenolate mofetil resulted in mean steady state (MPA AUC) values similar to those found in renal transplant patients administered mycophenolate mofetil 1 g bd oral.

Renal Impairment:

In a single dose study (six subjects per group), plasma (MPA AUCs) were up to 30% higher in subjects with mild to moderate renal impairment (GFR 25 - 80 mL/minute/1.73m^2) and 75% higher in subjects with severe renal impairment (GFR < 25 mL/minute/1.73m^2) than those subjects with normal renal function (GFR > 80 mL/minute/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 mycophenolate mofetil is increased from a daily dose of 2 to 3 g (see Section 4.2 Dosage and Method of Administration). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. In addition, the single dose plasma AUC of glucuronide of mycophenolic acid, was three to six 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 glucuronide of mycophenolic acid. No data are available on the safety of long-term exposure to this level of glucuronide of mycophenolic acid.

Delayed Renal Graft Function Post-Transplant:

In patients with delayed renal graft function post-transplant, mean $AUC_{(0-12)}$ of mycophenolic acid was comparable to that seen in post-transplant patients without delayed graft function. However, mean plasma $AUC_{(0-12)}$ of glucuronide of mycophenolic acid was two- to three-fold higher than post-transplant patients without delayed graft function. Also, with repeated dosing, plasma concentrations of glucuronide of mycophenolic acid accumulated, whereas accumulation of mycophenolic acid occurred to a lesser degree, if at all. High plasma concentrations of glucuronide of mycophenolic acid may displace mycophenolic acid from its protein binding sites resulting in a transient increase in the plasma concentration of free mycophenolic acid in patients with delayed graft function. No dose adjustment is recommended although close monitoring is advised.

Haemodialysis:

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

Hepatic Impairment:

In volunteers with alcoholic cirrhosis, hepatic glucuronide of mycophenolic acid 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 mycophenolic acid and glucuronide of mycophenolic acid were evaluated in 55 paediatric renal transplant patients aged 1 to 18 years given mycophenolate mofetil 600 mg/m^2. Mycophenolate mofetil orally twice daily (up to a maximum of 1 g bd). This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g bd in the early and late post-transplant period. MPA AUC levels across age groups were similar in the early post-transplant period out to nine months post-transplant. There is limited pharmacokinetic data available for children aged less than 2 years.

Plasma-Binding:

Mycophenolic acid, at clinically relevant concentrations, is 97% bound to plasma albumin. Glucuronide of mycophenolic acid (MPAG) is 82% bound to plasma albumin at glucuronide of mycophenolic acid concentration ranges such as those normally seen in stable renal transplant patients; however at higher concentrations of glucuronide of mycophenolic acid 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 mycophenolic acid to human serum albumin (HSA) or plasma proteins showed that salicylate (at 250 µ/mL with HSA) and glucuronide of mycophenolic acid (at greater than or equal to 460 µ/mL with plasma proteins) increased the free fraction of mycophenolic acid At concentrations that exceeded what is encountered clinically, naproxen, digoxin, cyclosporin, theophylline, tacrolimus, tolbutamide, propranolol, warfarin, and prednisone did not increase the free fraction of mycophenolic acid. Mycophenolic acid at concentrations as high as 100 µ/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

Mycophenolate mofetil did not induce point mutations (Ames assay) or primary DNA damage (yeast mitotic gene conversion assay) in the presence or absence of metabolic activation. Mycophenolate mofetil 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 µ/mL) that cause excessive cytotoxicity.

Carcinogenicity

A 104 week oral carcinogenicity study in mice with mycophenolate mofetil 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,

mycophenolate mofetil in daily doses up to 15 mg/kg (0.6 times the expected maximum clinical dose based on AUC values) was not tumorigenic.

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

Each 500 mg film coated tablet contains the excipients microcrystalline cellulose, povidone, hyprolose, croscarmellose sodium, purified talc, magnesium stearate and OPADRY complete film coating system 03B50110 PURPLE.

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 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

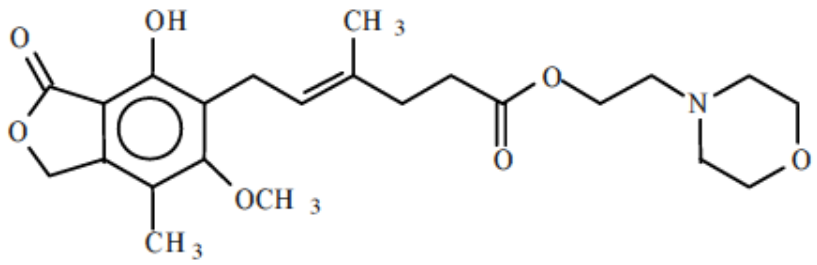
PVC/PVDC/Al blister packs of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid.

The chemical name for mycophenolate mofetil is2-(Morpholin-4-yl)ethyl (4E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

It has a molecular formula of $C_{23}H_{31}NO_7$ and a molecular weight of 433.50.

Mycophenolate mofetil 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 media (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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9 DATE OF FIRST APPROVAL

2 February 2011

10 DATE OF REVISION

20 August 2018

Summary table of changes

Section(s) changed	Summary of new information
n.a.	Reformatted Product Information
Title 3, 4.2, 4.3, 4.4, 4.5, 4.6, 4.9, 6.4 & 6.5 6.1 8	Trade Name change Removing reference to trade names and dosage form AAN usage Sponsor details updated