

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate mofetil Clonmel 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mycophenolate mofetil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Lavender coloured, capsule shaped, film-coated tablet, engraved with "APO" on one side and "MYC500" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycophenolate mofetil is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

4.2 Posology and method of administration

Treatment with Mycophenolate mofetil should be initiated and maintained by appropriately qualified transplant specialists.

The tablets should not be crushed or chewed.

Use in renal transplant:

Adults: Oral Mycophenolate mofetil therapy should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1.0 g administered twice daily (2 g daily dose).

Children and adolescents (aged 2 to 18 years): The recommended dose of mycophenolate mofetil is 600 mg/m² administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate mofetil tablets should only be prescribed to patients with a body surface area greater than 1.5 m², at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Children (<2 years): There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

Use in cardiac transplant:

Adults: Oral Mycophenolate mofetil therapy should be initiated within 5 days following cardiac transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Children: No data are available for paediatric cardiac transplant patients.

Use in hepatic transplant:

Adults: Intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral Mycophenolate mofetil therapy initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Children: No data are available for paediatric hepatic transplant patients.

Use in elderly patients (≥ 65 years): The recommended dose of 1.0 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Use in renal impairment: In renal transplant patients with severe chronic renal impairment (glomerular filtration rate $<25 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Use in severe hepatic impairment: No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes: MPA (mycophenolic acid) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of Mycophenolate mofetil is not required. There is no basis for Mycophenolate mofetil dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

4.3 Contraindications

Hypersensitivity reactions to mycophenolate mofetil have been observed (see section 4.8). Therefore, Mycophenolate mofetil is contraindicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid.

Hypersensitivity to any of the excipients.

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

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

4.4 Special warnings and precautions for use

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

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

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

Patients receiving Mycophenolate mofetil should be monitored for neutropenia, which may be related to Mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mycophenolate mofetil should have complete blood counts weekly during the first

month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $<1.3 \times 10^3/\mu\text{l}$), it may be appropriate to interrupt or discontinue Mycophenolate mofetil.

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

Patients 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). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

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

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

It is recommended that Mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

In view of the significant reduction in the AUC (area under the curve) of MPA by cholestyramine, caution should be used in the concomitant administration of Mycophenolate mofetil with medicinal products that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate mofetil.

The risk:benefit ratio of mycophenolate mofetil in combination with tacrolimus or sirolimus has not been established (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Aciclovir: Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was co-administered with aciclovir in comparison to the administration of that substance alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics were minimal (MPAG increased by 8%) and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids with magnesium and aluminium hydroxides: Absorption of mycophenolate mofetil was decreased when administered concomitantly with antacids.

Cholestyramine: Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA (see sections 4.4 and 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of Mycophenolate mofetil.

Medicinal products that interfere with enterohepatic circulation: Caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy of Mycophenolate mofetil.

Ciclosporin A: Ciclosporin A pharmacokinetics is not affected by Mycophenolate mofetil. In contrast, if concomitant ciclosporin treatment is stopped, an increase in MPA AUC of around 30% should be expected.

Ganciclovir: Based on the results of a single dose study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of Mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that concomitant administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and Mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in which Mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives: The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co-administration of Mycophenolate mofetil (see also section 5.2).

Rifampicin: in patients not also taking ciclosporin, concomitant administration of Mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust Mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sirolimus: in renal transplant patients, concomitant administration of Mycophenolate mofetil and CsA resulted in reduced MPA exposures by 30-50% compared with patients receiving the combination of sirolimus and similar doses of Mycophenolate mofetil (see also section 4.4).

Sevelamer: decrease in MPA C_{max} and AUC₀₋₁₂ by 30% and 25%, respectively, were observed when Mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer Mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There is no data on Mycophenolate mofetil with phosphate binders other than sevelamer.

Trimethoprim/sulfamethoxazole: No effect on the bioavailability of MPA was observed.

Norfloxacin and metronidazole: in healthy volunteers, no significant interaction was observed when Mycophenolate mofetil was concomitantly administered with norfloxacin and metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30 % following a single dose of mycophenolate mofetil.

Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of their discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tacrolimus: In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by coadministration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Other interactions: Concomitant administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

It is recommended that Mycophenolate mofetil therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate mofetil therapy, during therapy, and for six weeks following discontinuation of therapy (see section 4.5). Patients should be instructed to consult their physician immediately should pregnancy occur.

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

Lactation

Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse effects to mycophenolate mofetil in breast-fed infants, Mycophenolate mofetil is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

4.8 Undesirable effects

Very common	($\geq 1/10$)
Common	($\geq 1/100$ to $<1/10$)
Uncommon	($\geq 1/1,000$ to $<1/100$)
Rare	($\geq 1/10,000$ to $<1/1,000$)
Very rare	($<1/10,000$)
Not known	(cannot be estimated from the available data)

The following undesirable effects cover adverse reactions from clinical trials:

The principal adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis, and vomiting, and there is evidence of a higher frequency of certain types of infections (see section 4.4).

Malignancies:

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Lymphoproliferative disease or lymphoma developed in 0.6% of patients receiving mycophenolate mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6% of patients; other types of malignancy occurred in 1.1 % of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Opportunistic infections:

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4). The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were *Candida mucocutaneous*, cytomegalovirus (CMV) viraemia/syndrome and *Herpes simplex*. The proportion of patients with CMV viraemia/syndrome was 13.5%.

Children and adolescents (aged 2 to 18 years):

The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m² mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

Elderly patients (≥ 65 years):

Elderly patients (≥ 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 cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Other adverse reactions:

Adverse reactions, probably or possibly related to mycophenolate mofetil, reported in ≥ 1/10 and in ≥1/100 to <1/10 of patients treated with mycophenolate mofetil in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table.

Adverse Reactions, Probably or Possibly Related to mycophenolate mofetil, Reported in Patients Treated with mycophenolate mofetil in Renal, Cardiac and Hepatic Clinical Trials when Used in Combination with Ciclosporin and Corticosteroids

Within the system/organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class		Undesirable effects
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	Very common	–
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leucocytosis
Metabolism and nutrition disorders	Very common	–
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	–
	Common	Agitation, confusional state, depression, anxiety, abnormal thinking, insomnia
Nervous system disorders	Very common	–

	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	–
	Common	Tachycardia
Vascular disorders	Very common	–
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	–
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	–
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	–
	Common	Skin hypertrophy, rash, acne, alopecia
Musculoskeletal and connective tissue disorders	Very common	–
	Common	Arthralgia
Renal and urinary disorders	Very common	–
	Common	Renal impairment
General disorders and administration site conditions	Very common	–
	Common	Oedema, fever, chills, pain, malaise, asthenia
Investigations	Very common	–
	Common	Hepatic enzymes increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

Note: 501 patients (2 g mycophenolate mofetil daily), 289 patients (3 g mycophenolate mofetil daily) and 277 patients (2 g IV / 3 g oral mycophenolate mofetil daily) were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

The following undesirable effects cover adverse reactions from post-marketing experience: The types of adverse reactions reported during post-marketing with mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies. Additional adverse reactions reported during post-marketing are described below with the frequencies reported within brackets if known.

Gastrointestinal disorders: gingival hyperplasia ($\geq 1/100$ to $< 1/10$), colitis including cytomegalovirus colitis, ($\geq 1/100$ to $< 1/10$), pancreatitis, ($\geq 1/100$ to $< 1/10$) and intestinal villous atrophy.

Disorders related to immunosuppression: Serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil. Agranulocytosis ($\geq 1/1000$ to $< 1/100$) and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate mofetil, some of which have been fatal.

Blood and lymphatic system disorder: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

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

Hypersensitivity: Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction, have been reported.

Congenital disorders: For further details see section 4.6.

Respiratory, thoracic and mediastinal disorders: There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal.

4.9 Overdose

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 medicinal product.

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with Mycophenolate mofetil should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. By interfering with enterohepatic circulation of the medicinal product, bile acid sequestrants, such as colestyramine, reduce the MPA AUC (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents
ATC code L04AA06

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise "salvage" pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

5.2 Pharmacokinetic properties

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food.

Mycophenolate mofetil is not measurable systemically in plasma following oral administration. MPA at clinically relevant concentrations is 97% bound to plasma albumin. As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. A negligible amount of substance is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabelled mycophenolate mofetil results in complete recovery of the administered dose with 93% of the administered dose recovered in the urine and 6% recovered in the faeces. Most (about 87 %) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (>100 µg/ml), small amounts of MPAG are removed.

In the early post-transplant period (<40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Renal impairment:

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate <25 ml•min⁻¹•1.73 m⁻²) were 28 – 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC 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. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function:

In patients with delayed renal graft function post-transplant, mean MPA AUC (0–12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2- to 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of Mycophenolate mofetil does not appear to be necessary.

Hepatic impairment:

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

Children and adolescents (aged 2 to 18 years):

Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients given 600 mg/m² mycophenolate mofetil orally 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 BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Elderly patients (≥ 65 years):

The pharmacokinetics of mycophenolate mofetil in the elderly has not been formally evaluated.

Oral contraceptives:

The pharmacokinetics of oral contraceptives were unaffected by co-administration of mycophenolate mofetil (see also section 4.5). A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

5.3 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2

times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to $20 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats oral doses of $4.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ caused malformations (including anophthalmia, agnathia and hydrocephaly) in the offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

In teratology studies, foetal resorptions and malformations occurred in rats at $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (including anophthalmia, agnathia and hydrocephaly) and in rabbits at $90 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia) in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. (Refer to section 4.6.)

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose.

Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see section 4.8).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose microcrystalline
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating:

Opadry purple 20B50135IH
(composed of: hypromellose 3cP (E464),
hydroxypropylcellulose (E463),
titanium dioxide (E171),
macrogol 400,
hypromellose 50cP (E464),
iron oxide black (E172),
iron oxide red (E172)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Blister packs: 3 years.
HDPE bottles: 3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blisters: 50, 150 and 250 tablets.
HDPE bottles: 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, Mycophenolate mofetil tablets should not be crushed. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PA 126/195/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08th October 2010

10. DATE OF REVISION OF THE TEXT

April 2012