Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil Mylan 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mycophenolate mofetil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light pink film-coated, oval, biconvex, bevelled edge tablet debossed with “MYLAN” on one side of the tablet and “472” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mycophenolate Mofetil Mylan 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 Mylan should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Use in renal transplant:

Adults: oral Mycophenolate Mofetil Mylan should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Paediatric population (aged 2 to 18 years): the recommended dose of mycophenolate mofetil is 600 mg/m^2 administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate Mofetil Mylan should only be prescribed to patients with a body surface area greater than 1.5 m^2, 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.

Paediatric population (< 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 Mylan should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population: no data are available for paediatric cardiac transplant patients.

Use in hepatic transplant:

Adults: IV mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral Mycophenolate Mofetil Mylan 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).

Paediatric population: no data are available for paediatric hepatic transplant patients.

Elderly patients (≥ 65 years): the recommended dose of 1 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.

Patients with renal impairment: in renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 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.

Patients with 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 Mylan is not required. There is no basis for Mycophenolate Mofetil Mylan 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 Mylan is contraindicated in patients with a hypersensitivity to the active substance, mycophenolic acid or to any of the excipients listed in section 6.1.

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). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK-virus associated nephropathy, JC-virus associated progressive multifocal leukoencephalopathy (PML)). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. 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.

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

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

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 < $1.3 \times 10^3/\mu l$), 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 and Kelley-Seegmiller syndrome.

Use of mycophenolate mofetil during pregnancy is associated with an increased risk of congenital malformations. Mycophenolate mofetil therapy should not be initiated until a negative pregnancy test has been obtained (see section

4.6).

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 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 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

Aciclovir: higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8 %) were minimal 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 and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs vs. mycophenolate mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co- administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.

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 section 4.4 and section 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 (CsA) pharmacokinetics are unaffected 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 administration study of recommended doses of oral mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-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 coadministration 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 AUC 0-12 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: co-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 4.4).

Paediatric population

Interaction studies have only been performed in adults.

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).

Breast-feeding

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 reactions 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

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 1year 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, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5 %.

Paediatric population (aged 2 to 18 years):
The type and frequency of adverse reactions in a clinical study, which recruited 92 children and adolescents aged 2 to 18 years who were given 600 mg/m^2 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		**Adverse drug reactions**
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 (incl cysts and polyps)	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leucocytosis
Metabolism and nutrition disorders	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Common	Tachycardia
Vascular disorders	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	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	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Common	Skin hypertrophy, rash, acne, alopecia,
Musculoskeletal and connective tissue disorders	Common	Arthralgia
Renal and urinary disorders	Common	Renal impairment
General disorders and	Common	Oedema, pyrexia, chills, pain, malaise,

administration site conditions		asthenia,
Investigations	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

Note: 501 (2 g mycophenolate mofetil daily), 289 (3 g mycophenolate mofetil daily) and 277 (2 g IV / 3 g oral mycophenolate mofetil daily) patients 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.

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.

Blood and lymphatic system disorder:
Agranulocytosis (≥ 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.

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.

Immune system disorders: Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction have been reported. Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

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

Congenital, familial and genetic disorders: see further details in 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. There have also been reports of bronchiectasis in children and adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic re-circulation of the drug (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants ATC code L04AA06

Mechanism of action
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

Absorption
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.
Distribution
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 at clinically relevant concentrations, is 97 % bound to plasma albumin.
Biotransformation
MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.

Elimination
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 (> 100µg/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/1.73 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 – 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 – 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.

Paediatric population (aged 2 to 18 years):
Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients given 600 mg/m^2 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):
Pharmacokinetic behaviour 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 mg/kg/day. 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 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation 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 in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (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
Maize starch, pregelatinised
Povidone (K-30)
Silica, colloidal anhydrous
Magnesium stearate
Sodium lauril-sulfate
Croscarmellose sodium

Tablet coating:
Poly (vinyl alcohol)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Blisters: Store below 25°C. Store in the original container in order to protect from moisture.
Bottles: Store below 25°C. Store in the original container in order to protect from moisture.
Use within 90 days of opening. Once open keep bottle tightly closed.

6.5 Nature and contents of container

Round opaque HDPE bottle with a polypropylene child-resistant closure containing 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets. Bottle also contains canister of black activated carbon and silica gel granules (desiccant).

Round opaque HDPE bottle with a polypropylene fine ribbed closure containing 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets. Bottle also contains canister of black activated carbon and silica gel granules (desiccant).

Oblong opaque HDPE bottle with a polypropylene fine ribbed closure containing 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets. Bottle also contains canister of black activated carbon and silica gel granules (desiccant).

Amber Aclar-PVC/ Aluminium foil Blisters. Blister pack comprises of a transparent amber Aclar PVC film with backing of aluminium foil containing 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets.
Perforated blister pack comprises of a transparent amber Aclar PVC film with backing of aluminium foil containing 20x1, 50x1, 60x1, 120x1, 150x1, 180x1, 300x1, 450x1, 500x1 film coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd, T/A Gerard Laboratories,
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0577/126/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2011

10 DATE OF REVISION OF THE TEXT

February 2015