Public Assessment Report

Decentralised Procedure

Mycophenolate Mofetil 500 mg Film-coated Tablets

(Mycophenolate mofetil)

UK/H/2857/001/DC

PL 04569/0989

Generics [UK] Ltd
LAY SUMMARY

On 22 September 2010, the MHRA granted Generics [UK] Ltd a Marketing Authorisation (licence) for the medicinal product Mycophenolate Mofetil 500 mg Film-coated Tablets. This is a prescription-only medicine (POM).

Mycophenolate mofetil belongs to a group of medicines called immunosuppressants. These medicines are used to prevent your body rejecting a transplanted kidney, heart or liver. Mycophenolate mofetil is used together with other medicines known as ciclosporin and corticosteroids.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Mycophenolate Mofetil 500 mg Film-coated Tablets outweigh the risks. Hence, a Marketing Authorisation has been granted.
TABLE OF CONTENTS

Module 1: General Information  Page 4
Module 2: Summary of Product Characteristics  Page 5
Module 3: Product Information Leaflet  Page 21
Module 4: Labelling  Page 27
Module 5: Scientific Overview and Discussion  Page 33

   I. Introduction
   II. Quality aspects
   III. Non-clinical aspects
   IV. Clinical aspects
   V. Overall conclusion and Benefit-Risk Assessment

Module 6: Steps taken after initial procedure
## GENERAL INFORMATION

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Mycophenolate Mofetil 500 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>INN (or common name) of the active substance(s):</strong></td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic group (ATC Code):</strong></td>
<td>Immunosuppressive agent, ATC:LO4AA06</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength:</strong></td>
<td>Film-coated tablets, 500 mg</td>
</tr>
<tr>
<td><strong>Reference Number for the Decentralised Procedure</strong></td>
<td>UK/H/2857/001/DC</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Generics [UK] Ltd, Station Close, Potters Bar Hertforshire EN6 1TL United Kingdom</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>AT, EL, PT, BE, ES, RO, BG, FI, SE, FR, SI, CZ, SK, DE, IE, NL, DK, NO, IT, PL</td>
</tr>
<tr>
<td><strong>End of Procedure (day 160)</strong></td>
<td>31 August 2010</td>
</tr>
</tbody>
</table>
MODULE 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Mycophenolate Mofetil 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

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 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.

Use in renal transplant:

Adults: oral Mycophenolate Mofetil 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).

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 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 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).

Children: 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 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 (≥ 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.

Use in renal impairment: in renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²), 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 or to any of the excipients have been observed (see section 4.8). Therefore, Mycophenolate Mofetil is contraindicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid or 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 x 10^3/µl), 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

Interaction studies have only been performed in adults.

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 with magnesium and aluminium hydroxides: absorption of mycophenolate mofetil was decreased when administered 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 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 $C_{\text{max}}$ 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\text{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).

**4.6 Pregnancy and lactation**
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).

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 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, 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 children and adolescents 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 form the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Very common Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster</td>
</tr>
<tr>
<td>System organ class</td>
<td>Adverse drug reactions</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Common Skin cancer, benign neoplasm of skin</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common Leucopenia, thrombocytopenia, anaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common Tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common Hypotension, hypertension, vasodilatation</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common Pleural effusion, dyspnoea, cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common Vomiting, abdominal pain, diarrhoea, nausea</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Common Hepatitis, jaundice, hyperbilirubinaemia</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common Skin hypertrophy, rash, acne, alopecia,</td>
</tr>
</tbody>
</table>
System organ class | Adverse drug reactions
---|---
Musculoskeletal and connective Tissue disorders | Common | Arthralgia
Renal and urinary disorders | Common | Renal impairment
General disorders and administration site conditions | Common | Oedema, pyrexia, chills, pain, malaise, 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.

Gastrointestinal: 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.

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 (≥ 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**: 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.

### 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

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<sub>max</sub> 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 (> 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<sub>max</sub> 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<sup>2</sup>) 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.

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):
Pharmacokinetic behaviour of mycophenolate mofetil in the elderly has not been formally evaluated.

Oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by coadministration of mycophenolate mofetil (see also section 4.5). A study of the coadministration 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 $C_{\text{max}}$) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or $C_{\text{max}}$) 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
Croskemellose Sodium

Tablet coating:
Polyvinyl Alcohol
Titanium Dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron Red Oxide (E172)
Iron Yellow Oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blisters: 12 months
Bottles: 2 years (24 months)

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 bag of white activated 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 bag of white activated 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 bag of white activated silica gel granules (desiccant).

Amber Aclar-PVC/ Al-LDPE-Paper Peelable Unit Dose Blisters. Blister pack comprises of a transparent amber Aclar PVC film with backing of peelable
paper/LDPE/aluminium foil coated with a heat seal lacquer containing 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for 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
Generics [UK] Ltd
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04569/0989

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/09/2010

10 DATE OF REVISION OF THE TEXT
22/09/2010
PACKAGE LEAFLET: INFORMATION FOR THE USER

Mycophenolate Mofetil 500 mg Film-coated Tablets
mycophenolate mofetil

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Mycophenolate Mofetil is and what it is used for
2. Before you take Mycophenolate Mofetil
3. How to take Mycophenolate Mofetil
4. Possible side effects
5. How to store Mycophenolate Mofetil
6. Further information

1. WHAT MYCOPHENOLATE MOFETIL IS AND WHAT IT IS USED FOR

Mycophenolate Mofetil belongs to a group of medicines called immunosuppressants. These medicines are used to prevent your body rejecting a transplanted kidney, heart or liver. Mycophenolate Mofetil is used together with other medicines known as ciclosporin and corticosteroids.

2. BEFORE YOU TAKE MYCOPHENOLATE MOFETIL

Do not take Mycophenolate Mofetil:

- If you are allergic (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of Mycophenolate Mofetil.
- If you are breast-feeding.

Take special care with Mycophenolate Mofetil:

You should inform your doctor immediately:
- If you experience any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding.
- If you have or ever have had any problems with your digestive system, e.g., stomach ulcers.

Mycophenolate Mofetil reduces your body’s defence mechanism. Because of this, there is an increased risk of skin cancer. Therefore you should limit your exposure to sunlight and UV light by wearing appropriate protective clothing and using a sunscreen with a high protection factor.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed.

If you answer yes to any of the following questions talk to your doctor before you start to take Mycophenolate Mofetil:
- Are you taking any medicines containing: azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation), cholestyramine (used to
treat patients with high cholesterol), rifampicin (antibiotic), antacids, phosphate binders (used in patients with chronic renal failure to reduce the absorption of phosphate) or any other medicines (including those you can buy without a prescription) that your doctor does not know about?

- Do you need to receive vaccines (live vaccines)? Your doctor will have to advise you what is indicated for you.

**Taking Mycophenolate Mofetil with food and drink**
Taking food and drink has no influence on your treatment with Mycophenolate Mofetil.

**Pregnancy and breast-feeding**
Do not take Mycophenolate Mofetil if you are breast-feeding.

You must not use Mycophenolate Mofetil during pregnancy unless clearly indicated by your doctor. Your doctor should advise you about using contraception before taking Mycophenolate Mofetil, whilst taking Mycophenolate Mofetil, and for six weeks after you have stopped taking Mycophenolate Mofetil. This is because Mycophenolate Mofetil may cause spontaneous abortions or damage, including problems with development of the ears, to your unborn baby. Tell your doctor straight away if you are pregnant, breast-feeding, become pregnant or plan to start a family in the near future.

Ask your doctor for advice before taking any medication.

**Driving and using machines**
Mycophenolate Mofetil has not been shown to impair your ability to drive or operate machinery.

3. **HOW TO TAKE MYCOPHENOLATE MOFETIL**

Always take Mycophenolate Mofetil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual way to take Mycophenolate Mofetil is as follows:

**Kidney Transplant**
- **Adults:** The first dose will be given within 72 hours after the transplant operation. The recommended daily dose is 4 tablets (2 g of the active ingredient) taken as 2 separate doses. This means taking 2 tablets in the morning then 2 tablets in the evening.

- **Children (aged 2 to 18 years):** The dose given will vary depending on the size of the child. Your doctor will decide the most appropriate dose based on body surface area (height and weight). The recommended dose is 600 mg/m² taken twice a day.

**Heart Transplant**
- **Adults:** The first dose will be given within 5 days following the transplant operation. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning then 3 tablets in the evening.

- **Children:** No data are available to recommend the use of Mycophenolate Mofetil in children who have received a heart transplant.

**Liver Transplant**
- **Adults:** The first dose of oral Mycophenolate Mofetil will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medications. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning and 3 tablets in the evening.

- **Children:** No data are available to recommend the use of Mycophenolate Mofetil in children who have received a liver transplant.

**Method and route of administration**
Swallow your tablets whole with a glass of water. Do not break or crush them.

Treatment will continue for as long as you need immunosuppression to prevent you rejecting your transplanted organ.

If you take more Mycophenolate Mofetil than you should

If you take more tablets than you have been told to take, or if someone else accidentally takes your medicine, immediately see a doctor or go to a hospital straight away.

If you forget to take Mycophenolate Mofetil

If you forget to take your medicine at any time, take it as soon as you remember, then continue to take it at the usual times.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Mycophenolate Mofetil

Stopping your treatment with Mycophenolate Mofetil may increase the chance of rejection of your transplanted organ. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Mycophenolate Mofetil can have side effects, although not everybody gets them. Children may be more likely than adults to have side effects such as diarrhoea, infections, fewer white cells and fewer red cells in the blood.

The frequencies are defined as

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100
Uncommon: affects 1 to 10 users in 1,000
Rare: affects 1 to 10 users in 10,000
Very rare: affects less than 1 user in 10,000
Not known: frequency cannot be estimated from the available data

Very common side effects:
- Diarrhoea, vomiting, feeling sick, stomach pain
- Decrease in the normal amounts of different blood cells, which can result in frequent infections, bruising, bleeding, breathlessness and weakness
- Bacterial, fungal and viral infections of the digestive and urinary tract, cold sores and shingles

Common side effects:
- Changes in different laboratory parameters, including increase in liver enzymes, renal parameters such as creatinine, potassium, blood sugar, blood lipids, cholesterol, phosphates, magnesium, calcium and uric acid
- Altered blood count (increased or decreased number of cells in the blood)
- Kidney problems with increased levels of urea
- Disorders of the digestive system such as constipation, indigestion, excessive wind, belching, inflammation of the mouth, oesophagus, stomach, intestine, liver or pancreas and gastrointestinal bleeding
- Convulsions, increased tension in the muscles, shaking and muscle weakness, joint pain
- Confusion, agitation, depression, anxiety, sleeplessness, dizziness and headache, tingling or numbness, change of the sense of taste, loss of appetite, weight loss
- Inflammation and infections of the respiratory and gastrointestinal tract, sore throat, inflammation
of the sinuses, runny and itchy nose
- Skin cancer or non cancerous growths of the skin and fungal infections of the skin and vagina, acne, hair loss and rashes
- Changes in blood pressure, faster heart beat, dilation of blood vessels
- Shortness of breath, cough, fluid on lungs/chest cavity, gout
- Fluid retention in the body, fever, discomfort, lethargy, weakness and enlargement of the gums
- Inflammation of the liver, yellowing of the skin and whites of the eyes

Uncommon side effects:
- Proliferation of the lymphatic tissue, including malignant tumours
- Inflammation or infections of the heart and its valves and of the membrane that covers the brain and spinal cord
- Severe reduction in the number of white blood cells, which makes infections more likely (agranulocytosis)

Not known:
- Hypersensitivity (allergic) reactions, including wheezing or difficulty breathing, difficulty swallowing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives on the skin
- Severe infection of the brain cells (Progressive Multifocal Leuкоencephalopathy)
- Abnormal scarring and thickening of the lung tissue, causing shortness of breath.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet whilst you are taking Mycophenolate Mofetil, please tell your doctor or pharmacist. However, do not stop taking your medicine unless you have discussed this with your doctor first.

5. HOW TO STORE MYCOPHENolate MOFETIL

Keep out of the reach and sight of children.

Do not use the tablets after the expiry date, which is stated on the carton, blister and bottle after EXP. The expiry date refers to the last day of that month.

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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Mycophenolate Mofetil contains
- The active substance is mycophenolate mofetil. Each film-coated tablet contains 500 mg mycophenolate mofetil.
The other ingredients are: Tablet core: cellulose, microcrystalline; maize starch, pregelatinised; povidone (K-30); silica, colloidal anhydrous; magnesium stearate; sodium lauril sulfate; croscarmellose sodium Table coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b), iron red oxide (E172), iron oxide yellow (E172).

What Mycophenolate Mofetil looks like and contents of the pack

Your medicine is in the form of a film-coated tablet.

Mycophenolate Mofetil 500 mg Film-coated Tablets are light pink coloured, oval-shaped tablet engraved with “5” on one side of the tablet and “472” on the other side.
Mycophenolate Mofetil 500 mg Film-coated Tablets are available in blisters packs and bottles of 20, 50, 60, 120, 150, 180, 300, 450, 500 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

[To be completed nationally]

**This medicinal product is authorised in the Member States of the EEA under the following names:**

[To be completed nationally]

**This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil 500 mg Film-coated Tablets
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains mycophenolate mofetil 500 mg

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated Tablets
20 film-coated tablets
50 film-coated tablets
60 film-coated tablets
120 film-coated tablets
150 film-coated tablets
180 film-coated tablets
300 film-coated tablets
450 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not crush or chew

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
<table>
<thead>
<tr>
<th></th>
<th>OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>EXPIRY DATE</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
<tr>
<td>9</td>
<td>SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td></td>
<td>Blister carton: Store below 25°C. Store in the original container in order to protect from moisture.</td>
</tr>
<tr>
<td></td>
<td>Bottle carton: 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.</td>
</tr>
<tr>
<td>10</td>
<td>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td></td>
<td>Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.</td>
</tr>
<tr>
<td>11</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
<tr>
<td>12</td>
<td>MARKETING AUTHORISATION NUMBER(S)</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
<tr>
<td>13</td>
<td>BATCH NUMBER</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
<tr>
<td>14</td>
<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
<tr>
<td>15</td>
<td>INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td></td>
<td>[To be completed nationally]</td>
</tr>
</tbody>
</table>
16. INFORMATION IN BRAILLE

Mycophenolate Mofetil Mylan 500 mg Film-coated Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil 500 mg Film-coated Tablets
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains mycophenolate mofetil 500 mg

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated Tablets
20 film-coated tablets
50 film-coated tablets
60 film-coated tablets
120 film-coated tablets
150 film-coated tablets
180 film-coated tablets
300 film-coated tablets
450 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not crush or chew
6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

[To be completed nationally]

9. **SPECIAL STORAGE CONDITIONS**

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.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

[To be completed nationally]

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**
16. INFORMATION IN BRAILLE

Mycophenolate Mofetil 500 mg Film-coated Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil 500 mg Film-coated Tablets
mycophenolate mofetil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

[To be completed nationally]

4. BATCH NUMBER

[To be completed nationally]

5. OTHER
MODULE 5

SCIENTIFIC OVERVIEW AND DISCUSSION

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mycophenolate Mofetil 500 mg Film-coated Tablets, in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants could be approved.

Problem statement
This decentralised application concerns a generic version of mycophenolate mofetil under the trade name Mycophenolate Mofetil 500 mg Film-coated Tablets.

The originator product is Cellcept (500 mg tablets) by Roche Registration Ltd., registered via the centralised procedure in the EU since 14 February 1996.

With the UK as the Reference Member State in this decentralised procedure, Qualimed is applying for a Marketing Authorisation for Mycophenolate Mofetil 500 mg Film-coated Tablets in BE, FR, LU, NL.

About the product
Successful organ transplantation is reliant on the use of immunosuppressant agents that prevent organ rejection, reverse acute rejection and prevent and treat graft versus host disease. Mycophenolate Mofetil 500 mg Film-coated Tablets are indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate mofetil is quickly and completely hydrolysed into its active metabolite mycophenolic acid (MPA) following oral administration.

MPA is a selective, non competitive, reversible inhibitor of inosine 5’-monophosphate dehydrogenase (IMPDH), the rate limiting enzyme in the de novo synthesis of intracellular guanosine. MPA has selectivity towards the inhibition of lymphocyte proliferation as T and B lymphocyte proliferation depends entirely on the de novo synthesis of purines. Lymphocytes have a significant role in the pathophysiology of acute transplant rejection. MPA has selectivity towards the inhibition of activated lymphocytes. Hence, selective inhibition of lymphocytes may reduce acute rejection whilst leaving other cells to defend against infection and malignancy. Triple therapy immunosuppressive regimens which include mycophenolate mofetil, cyclosporin A and steroids are superior as compared to conventional regimens, which include azathioprine, cyclosporin A and steroids in renal transplant patients.

The measurement of mycophenolate mofetil in blood after its oral administration is difficult due to its rapid conversion to MPA. The mean apparent plasma half life is similar following oral and intravenous routes of administration at approximately 17 hours and the plasma clearance is 11.6L/h after oral administration. There is no clinical effect of the presence or absence of food.
**General comments on the submitted dossier**
The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with current EU regulatory requirements. Satisfactory quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles**
The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal version of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal version of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS and CMS considered that the application could be approved with the end of procedure (Day 160) on 31 August 2010. After a subsequent national phase, the licence was granted in the UK on 22 September 2010.

### II QUALITY ASPECTS

**Drug substance**

**General Information**

Structure:

![Mycophenolate Mofetil Structure](image)

Description: White to off-white, crystalline powder
Solubility: Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.
Chemical names: 2-(morpholin-4-yl)ethyl-(4\(E\))-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl-4-methylhex-4-enolate
mycophenolic acid 2-(4-morpholinyl)ethyl ester
INN: mycophenolate mofetil
Molecular formula: C\(_{23}\)H\(_{31}\)NO\(_7\)
MW: 433.5
The chemical-pharmaceutical documentation and Expert Report in relation to Mycophenolate Mofetil 500 mg Film-coated Tablets are of sufficient quality in view of the present European regulatory requirements. The drug substance mycophenolate mofetil is the subject of a monograph in the European Pharmacopoeia. The drug substance specification for the drug substance is acceptable. Stability studies have been performed. No significant changes in any parameters were observed. The proposed re-test period for the drug substance is considered acceptable.

**Drug Product**

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validation reports for the analytical methods have been presented. Batch analysis has been performed and the results show that the finished product meets the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Based on the stability data a proposed shelf-life of 12 months and 24 months when stored in Al/LDPE/paper blister and HDPE bottles respectively is considered acceptable, with an in-use shelf life of 90 days for the bottled product.

**III NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of mycophenolate mofetil are well known. As mycophenolate mofetil is a well known drug substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by an appropriately qualified toxicologist. The overview is dated August 2009 and refers to 27 references from the published literature dated up to 2009. The overview is considered acceptable in view of the fact that the toxicological properties of mycophenolate mofetil are well known.

There are no objections to the approval of Mycophenolate Mofetil 500 mg Film-coated Tablets from a non-clinical point of view.

**IV CLINICAL ASPECTS**

**Clinical study reports**

To support the application, the applicant has submitted data from a comparative bioequivalence study comparing generic Mycophenolate Mofetil 500 mg Film-coated Tablets with Cellcept 500 mg tablets.

**Methods**

**Study design**

A randomised, single dose, open label, two treatment, two period, two sequence, cross over, comparative bioavailability study of Mycophenolate Mofetil 500 mg Film-coated Tablets and Cellcept 500 mg tablets (Roche Limited, UK) was carried out. The study was conducted in compliance with ICH-GCP guidelines and the Declaration of
Helsinki. The final protocol was approved by the independent ethics committee on 25 February 2009.

Healthy non-smoking male and female (not of child-bearing potential) volunteers aged 18-55 years (inclusive), were enrolled. The study was conducted in the fasting state. Of a total of 36 subjects were enrolled, 33 completed the study and were enrolled into the pharmacokinetic analysis. Subjects were fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours after dosing. There was a washout period of 7 days and two treatment periods. The test product was administered as a single oral dose of 1000 mg (2 x 500 mg tablets) with 240 ml of water. The reference product was administered as a single oral dose of 1000 mg (2 x 500 mg tablets) with 240 ml of water.

Blood samples were collected before dosing and at intervals up to and including 72 hours post-dose. The primary efficacy variables were C max, AUC0-t and AUC0-∞ for mycophenolic acid.

**Results**

Thirty-six volunteers were enrolled in the study. Subject eight withdrew consent during period one, subject 10 did not report for period two dosing and subject 28 withdrew prior to period two dosing.

According to the data presented, the mycophenolic acid 90 % confidence intervals for C max, AUC0-∞ and AUC0-t are within the predefined interval of 80.00-125.00 %. Bioequivalence has been demonstrated between the test and reference products. Results have been provided to two decimal places as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCL</td>
<td>95.95% – 104.35%</td>
</tr>
<tr>
<td>AUCI</td>
<td>94.35% – 104.79%</td>
</tr>
<tr>
<td>CPEAK</td>
<td>90.58% – 116.45%</td>
</tr>
</tbody>
</table>

The applicant states that as a result of enterohepatic recycling of MPA, KEL could not be reliably determined in all subjects, hence determination of AUCI was based on those 27 subjects who had KEL values for both products. This is accepted. The applicant has clarified that for all subjects for whom KEL could be determined the residual extrapolated area was <20%. In three subjects for whom KEL could not be
determined this was >20%, however, as sampling was carried out for 72 hours this is accepted. The applicant has clarified that 33 subjects were included in the calculation of AUCL and Cpeak because three subjects did not complete the study. Twenty-seven subjects were used in the determination of AUCI.

The estimated intra-subject coefficient of variation observed in the study was as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intra-subject coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>30.8%</td>
</tr>
<tr>
<td>AUCL</td>
<td>10.1%</td>
</tr>
<tr>
<td>AUCI</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Safety
The safety assessment included information from all 36 subjects who received at least one dose of study medication during the study. No serious events were reported. No adverse events were reported throughout the study period. Over the course of the study, there were no clinically significant changes in the clinical laboratory measurements that could be reasonably associated with the formulations under investigation.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study in which the following 90% confidence intervals for mycophenolic acid were observed; AUC$_{0-t}$ 96-104%, AUC$_{0-\infty}$ 94-105% and C$_{\text{max}}$ 91-116%. Mycophenolate Mofetil 500 mg Film-coated Tablets is considered bioequivalent to Cellcept 500 mg Tablets (Roche Ltd).

Pharmacodynamics
No new data have been submitted and none are required for this generic application.

Clinical efficacy
No new data have been submitted and none are required for this generic application.

Clinical safety

Pharmacovigilance system
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
A risk management plan is not required as the product is a generic product with a well recognised acceptable adverse events profile.

Periodic Safety Update Report (PSUR)
Since mycophenolate mofetil is a well known active substance, which has been marketed for many years throughout the EU, the applicant has applied for a PSUR
submission scheme of 3 years upon approval. This suggestion is acceptable. Mycophenolate mofetil is found in the list published by the Heads of Medicines Agencies with an EU Harmonised Birthday and related Data Lock Point (DLP). The suggestion is acceptable because the innovator product has a 3 year PSUR submission scheme and this period should be followed.

Clinical Conclusion

In the submitted bioequivalence study, the 90% confidence intervals of the test to reference product for \( \text{ln-} \text{transformed } \text{AUC}_0-t, \text{AUC}_0-\text{inf} \) and \( C_{\text{max}} \) lie within the acceptance range of 80.00 % to 125.00 %. Mycophenolate Mofetil 500 mg Film-coated Tablets is therefore considered bioequivalent to Cellcept 500 mg Tablets (Roche Ltd).

The use of Mycophenolate Mofetil is well established in the EU. When used in the licensed indications it has recognised efficacy and an acceptable safety profile. With regards to the current application, the risk: benefit analysis for Mycophenolate Mofetil 500 mg Film-coated Tablets is favourable.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Mycophenolate Mofetil 500 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant’s Mycophenolate Mofetil 500 mg Film-coated Tablets and its respective reference product.

SAFETY

No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mycophenolate mofetil is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is therefore considered to be positive.
## MODULE 6

### STEPS TAKEN AFTER INITIAL PROCEDURE

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>