Public Assessment Report

Decentralised Procedure

MYCOPHENOLATE MOFETIL 500 MG FILM-COATED TABLETS

UK/H/3640/001/DC
UK Licence No: PL 35646/0001

ALKEM PHARMA GMBH
LAY SUMMARY

On 6th October 2010, the UK granted Alkem Pharma GmbH a Marketing Authorisation (licence) for Mycophenolate Mofetil 500 mg Film-coated Tablets (PL 35646/0001; UK/H/3640/001/DC).

The active ingredient in this medicine is mycophenolate mofetil. Mycophenolate Mofetil is a medicine that is used to suppress immune activity.

Mycophenolate Mofetil is used to prevent your body rejecting a transplanted kidney, heart or liver. It is used in combination with other medicines with a similar function (i.e. 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 this Marketing Authorisation has been granted.
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### Module 1

<table>
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<tr>
<th><strong>Product Name</strong></th>
<th>Mycophenolate Mofetil 500 mg Film-coated Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Mycophenolate Mofetil</td>
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<tr>
<td><strong>Form</strong></td>
<td>Film-coated Tablets</td>
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<tr>
<td><strong>Strength</strong></td>
<td>500 mg</td>
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</table>
| **MA Holder** | Alkem Pharma GmbH  
Mainzer Landstraße 47,  
60329 Frankfurt am Main  
Germany |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | France (FR), Germany (DE), Italy (IT), Poland (PL) Spain (ES) |
| **Procedure Number** | UK/H/3640/001/DC |
| **End of Procedure** | Day 210 – 9th September 2010 |
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 film-coated tablet contains Mycophenolate Mofetil 500 mg.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet.
Lavender coloured caplet shaped biconvex film coated tablets debossed with ‘265’ on one side and plain on 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 500mg Tablets should only be prescribed to patients with a body surface area greater than 1.5 m², at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

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

Use in cardiac transplant:
Adults: Oral Mycophenolate Mofetil 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.

Consideration should be given to reducing the total immunosuppression, in patients who develop PML. In transplant patients, however, reduced immunosuppression may place the graft at risk.

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 10^9/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 AUC0-12 by 30% and 25%, respectively, were observed when Mycophenolate Mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer Mycophenolate Mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There is no data on Mycophenolate Mofetil with phosphate binders other than sevelamer.

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

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

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

Tacrolimus: in hepatic transplant patients initiated on Mycophenolate Mofetil and tacrolimus, the AUC and $C_{\text{max}}$ 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 paediatric patients aged 2 to 18 years who were given 600 mg/m² mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g Mycophenolate Mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

Elderly patients (≥ 65 years):

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving Mycophenolate Mofetil as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Other adverse reactions:

Adverse reactions, probably or possibly related to Mycophenolate Mofetil, reported in ≥ 1/10 and in ≥ 1/100 to < 1/10 of patients treated with Mycophenolate Mofetil in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table. Adverse Reactions, Probably or Possibly Related to Mycophenolate Mofetil, Reported in Patients Treated with Mycophenolate Mofetil in Renal, Cardiac and Hepatic Clinical Trials when Used in Combination with Ciclosporin and Corticosteroids

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>Leucopenia, thrombocytopenia, anaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal and connective Tissue disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Investigations</td>
<td>Very common</td>
<td>-</td>
</tr>
</tbody>
</table>

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 recirculation of the drug (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: immunosuppressive agents, ATC code: L04AA06
Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

5.2 Pharmacokinetic properties
Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of Mycophenolate Mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax 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_{max} approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Renal impairment:
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml•min^{-1}•1.73m^{-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.

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

Tablets Core:
- Cellulose microcrystalline
- Povidone (K-90)
- Croscarmellose sodium
- Magnesium stearate

Tablet coat:
- Hydroxypropyl methylcellulose
- Titanium dioxide (E171)
- Polyethylene glycol 400
- Polyethylene glycol 6000
- Red iron oxide (E172)
- Black iron oxide
- Yellow iron oxide

6.2 Incompatibilities

Not applicable
6.3 Shelf life
2 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVdC coated PVC film/Aluminium blisters in pack sizes of 50 or 150 tablets per carton.

6.6 Special precautions for disposal
Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, Mycophenolate Mofetil 500 mg Film-coated Tablets should not be crushed. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
ALKEM PHARMA GmbH
Mainzer Landstraße 47,
60329 Frankfurt am Main
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 35646/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/10/2010

10 DATE OF REVISION OF THE TEXT
06/10/2010
Module 3

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

Mycophenolate Mofetil is a medicine that is used to suppress immune activity. Mycophenolate Mofetil is used to prevent your body rejecting a transplanted kidney, heart or liver. It is used in combination with other medicines with a similar function (i.e. ciclosporin and corticosteroids).

2. BEFORE YOU TAKE MYCOPHENOLATE MOFETIL

Do not take Mycophenolate Mofetil:
- If you are allergic (hypersensitive) to Mycophenolate Mofetil, mycophenic acid or any of the other ingredients in Mycophenolate Mofetil Tablets.
- If you are breastfeeding.

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 defense mechanism and may increase the risk of developing 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.

- 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 breastfeeding.
Ask your doctor for advice before taking any medicine. 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.

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

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

Dosage
Always use 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.
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?

If you take more Mycophenolate Mofetil than you should:
If you take more tablets than you have been told or if someone else accidentally takes your medicine, immediately see doctor or go to the nearest hospital Accident and Emergency department.

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 cause 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. Tell your doctor or go to a hospital immediately if you experience any of the following side effects:
Very common side effects (likely to affect more than 1 in 10 people):
- Diarrhoea, vomiting, feeling sick, stomach pain
- Decrease in normal amounts of different blood cells, which can result in increased risk of infections, bruising, bleeding, breathlessness and weakness
- Bacterial, fungal and viral infections of the digestive and urinary tract, cold sores and shingles

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 then 3 tablets in the evening.

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

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

- and its valves and of the membrane that covers the brain and spinal cord
- Infection of the brain

Other side effects that have been reported where frequency has not been established:
- Hypersensitivity (allergic reactions) including shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash or itching

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.

5. HOW TO STORE MYCOPHENOLATE MOFETIL
Keep out of the reach and sight of children.

Do not use the tablets after the expiry date stated on the carton after EXP.

This medicine does not require any special storage conditions. Keep in outer carton in order to protect from light.

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 tablet contains 500 mg mycophenolate mofetil.
- The other ingredients are:
  Tablet core:
  Cellulose microcrystalline
  Povidone
  Croscarmellose sodium
  Magnesium stearate
Common side effects (likely to affect less than 1 in 10 people):
- 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
- Gout
- Kidney problems with increased levels of urea
- Disorders of the digestive system such as constipation, indigestion, flatulence, 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
- Sleeplessness dizziness and headache, tingling or numbness, change of the sense of taste, loss of appetite, weight loss, confusion, agitation, depression, anxiety, Abnormal thinking
- Inflammation and infections of the respiratory and gastrointestinal tract, sore throat, inflammation of the sinuses, runny and itchy nose, shortness of breath, fluid on the lungs, cough, gastrointestinal ulcers, increase in bilirubin
- Skin cancer or non cancerous growth of the skin and fungal infections of the skin and vagina, acne, hair loss, rashes
- Changes in blood pressure, faster heart beat, dilation of blood vessels, decrease in blood cell count or increase in white blood cell count
- Fluid retention in the body, fever, discomfort, lethargy and weakness
- Inflammation of the liver, yellowing of the skin and whites of the eyes

Uncommon side effects (likely to affect less than 1 in 100 people):
- Proliferation of the lymphatic tissue, including malignant tumours
- Inflammation or infections of the heart

Tablet coating:
Hydroxypropyl methylcellulose
Titanium dioxide (E171)
Polyethylene glycol 400
Polyethylene glycol 6000
Red iron oxide (E172)
Black iron oxide (E172)
Yellow iron oxide (E172)

What Mycophenolate Mofetil looks like and contents of the pack:
Mycophenolate Mofetil is supplied as lavender coloured, oval shaped coated tablet marked with “265” on one side and plain on the other side.
The tablets are presented in blister packs and supplied in packs of 50 or 150 tablets per carton.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
ALKEM PHARMA GmbH
Mainzer Landstraße 47,
60329 Frankfurt am Main
Germany

Manufacturer
ALKEM LABORATORIES LTD.
Village Thana, Baddi,
Himachal Pradesh - 173205
India

The leaflet was last approved in 24/08/2010.
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, France, Germany, Italy, Poland, Spain and the UK considered that the application for Mycophenolate Mofetil 500 mg Film-coated Tablets could be approved. These products are prescription only medicines (POM) indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

This application for Mycophenolate Mofetil 500 mg Film-coated Tablets was submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of CellCept 500 mg tablets which was granted in the EEA on 14th February 1996 to Roche Registration Limited.

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.

No new non-clinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of mycophenolate mofetil is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

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.

A satisfactory justification has been provided for non-submission of a Risk Management Plan (RMP) has been provided.
**II. ABOUT THE PRODUCT**

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<th>Name of the product in the Reference Member State</th>
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<td>Name and address of the authorisation holder</td>
<td>Alkem Pharma GmbH</td>
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<td>Mainzer Landstraße 47,</td>
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<td></td>
<td>60329 Frankfurt am Main</td>
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<td>Germany</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Mycophenolate Mofetil

Chemical name:

- 2-(morpholin-4-yl)ethyl-(4E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl-4-methylhex-4-enoate
- mycophenolic acid 2-(4-morpholinyl)ethyl ester

Structural formula:

Molecular formula: $\text{C}_{23}\text{H}_{31}\text{NO}_7$

Appearance: A white to off-white, crystalline powder.

Molecular weight: 433.5

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients inside the tablet core consist of pharmaceutical excipients cellulose microcrystalline, povidone (K-90), croscarmellose sodium, magnesium stearate.

The ingredients in the tablet coating are pharmaceutical excipients hydroxypropyl methylcellulose, titanium dioxide (E171), polyethylene glycol 400, polyethylene glycol 6000, red iron oxide (E172), black iron oxide and yellow iron oxide.
With the exception of red iron oxide (E172), black iron oxide and yellow iron oxide, all excipients comply with their respective European Pharmacopoeia monograph. Red iron oxide (E172), black iron oxide and yellow iron oxide comply with their United States Pharmacopoeia (USP) monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to produce a safe, efficacious product containing mycophenolate mofetil that could be considered a generic medicinal product of CellCept 500 mg tablets which was granted in the EEA on 14th February 1996 to Roche Registration Limited.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative impurity and *in vitro* dissolution profiles have been provided for the proposed and originator products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial-scale batches have been provided. The results are satisfactory.

**Finished Product Specification**

The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

These products are packaged in polyvinylidene chloride (PVdC) coated polyvinyl chloride (PVC) film and aluminium blisters further packaged into cartons.

The product comes in pack sizes of 50 or 150 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**

Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with no special storage instructions.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of mycophenolate mofetil are well-known. As mycophenolate mofetil is widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification has been provided for non-submission of an environmental risk assessment.

It is recommended that a Marketing Authorisation is granted for this application.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics
A single-dose, open-label, randomised, two-period, two-treatment, two-sequence, crossover study to compare the pharmacokinetics of the test product Mycophenolate Mofetil 500 mg tablets versus the reference product CellCept 500 mg tablets (Roche Registration Limited) in healthy subjects under fasted conditions.

A dose of the assigned product was administered after a fast of at least 10 hours. Blood samples were taken pre- and up to 72 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for mycophenolic acid are presented below as log-transformed values:

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<td>25065.20</td>
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<tr>
<td>T/R Ratio (90% CI)</td>
<td>(93.29 – 103.05)</td>
<td>(92.46 – 103.44)</td>
<td>(90.04 – 98.38)</td>
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The use of mycophenolic acid for assessment of the primary pharmacokinetic parameters is acceptable as mycophenolate mofetil is quickly and completely hydrolysed into its active metabolite mycophenolic acid (MPA) following oral administration.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC₀−₄ and C_max for the metabolite of mycophenolate mofetil, mycophenolic acid lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new efficacy data were submitted with this application and none were required.

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
MAA FORM
The MAA Form is medically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application.
IV 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 the reference product CellCept 500 mg tablets (Roche Registration Limited).

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical 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 benefit-risk is, therefore, considered to be positive.
## Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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