Public Assessment Report

Decentralised Procedure

Mycophenolate Mofetil 250mg Capsules

PL 17780/0323

UK/H/1843/01/DC

Winthrop Pharmaceuticals UK Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Winthrop Pharmaceuticals UK Limited a Marketing Authorisation (licence) for the medicinal product Mycophenolate Mofetil 250mg Capsules (product licence number: 17780/0323). This medicine is available on prescription only.

Mycophenolate Mofetil 250mg Capsules are used to prevent your body from rejecting a transplanted kidney, heart or liver. Mycophenolate Mofetil is used together with other medicines known as ciclosporin and corticosteroids.

The data submitted in support of this application for Mycophenolate Mofetil 250mg Capsules raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

### Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Mycophenolate Mofetil 250mg Capsules</th>
</tr>
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<tbody>
<tr>
<td>Type of application (Eudratrack details)</td>
<td>Level 1 Abridged</td>
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<tr>
<td></td>
<td>Level 2 Initial</td>
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<td>Level 3 10.1</td>
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<td>(L04AA06)</td>
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<td>18 November 2009</td>
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<td></td>
<td>One Onslow Street</td>
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<td>Surrey</td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Mycophenolate Mofetil 250mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 250 mg mycophenolate mofetil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard.
Mycophenolate Mofetil 250 mg Capsules: light blue/peach, size ‘1’ hard gelatin capsule imprinted with ‘MMF’ on cap and ‘250’ on body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Mycophenolate Mofetil 250 mg Capsules are 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 250 mg Capsules should be initiated and maintained by appropriately qualified transplant specialists.

Use in renal transplant:
Adults: oral Mycophenolate Mofetil 250 mg Capsules should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1.0 g administered twice daily (2 g daily dose).

Children and adolescents (aged 2 to 18 years): the recommended dose of mycophenolate mofetil is 600 mg/m² administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate Mofetil 250 mg Capsules should only be prescribed to patients with a body surface area of at least 1.25 m². Patient with a body surface area of 1.25 to 1.5 m² may be prescribed Mycophenolate Mofetil 250 mg Capsules at a dose of 750 mg twice daily (1.5g daily dose). Patient with a body surface area greater than 1.5m² may be prescribed Mycophenolate Mofetil 250 mg Capsules 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. There are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

Use in cardiac transplant:
Adults: oral Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules 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 1.0 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Use in renal impairment: in renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml\(\text{min}^{-1}\times1.73\text{ m}^{-2}\), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. Use in severe hepatic impairment: no dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes: MPA (mycophenolic acid) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of Mycophenolate Mofetil 250 mg Capsules is not required. There is no basis for Mycophenolate Mofetil 250 mg Capsules dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

4.3 Contraindications
Hypersensitivity reactions to Mycophenolate Mofetil 250 mg Capsules have been observed (see section 4.8). Therefore, Mycophenolate Mofetil 250 mg Capsules are contraindicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid. Mycophenolate Mofetil 250 mg Capsules are 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 250 mg Capsules, 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 250 mg Capsules 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, 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 250 mg Capsules should be monitored for neutropenia, which may be related to Mycophenolate Mofetil 250 mg Capsules itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mycophenolate Mofetil 250 mg Capsules 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 10⁹/µl) it may be appropriate to interrupt or discontinue Mycophenolate Mofetil 250 mg Capsules.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Mycophenolate Mofetil 250mg Capsules 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 250mg Capsules therapy. Changes to Mycophenolate Mofetil 250mg Capsules 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 250 mg Capsules 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 250 mg Capsules have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation, Mycophenolate Mofetil 250 mg Capsules should be administered with caution in patients with active serious digestive system disease.

Mycophenolate Mofetil 250 mg Capsules are 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.

It is recommended that Mycophenolate Mofetil 250 mg Capsules 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 colestyramine, caution should be used in the concomitant administration of Mycophenolate Mofetil 250 mg Capsules with medicinal products that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate Mofetil 250 mg Capsules. 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 each substance 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.

Colestyramine: following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of colestyramine 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 250 mg Capsules.

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 250 mg Capsules.

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 250 mg Capsules (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 are anticipated and Mycophenolate Mofetil 250 mg Capsules dose adjustment is not required. In patients with renal impairment in which Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules (see also section 5.2).
**Rifampicin:** in patients not also taking ciclosporin, concomitant administration of Mycophenolate Mofetil 250 mg Capsules and rifampicin resulted in a decrease in MPA exposure (AUC0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust Mycophenolate Mofetil 250 mg Capsules doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

**Sirolimus:** in renal transplant patients, concomitant administration of Mycophenolate Mofetil 250 mg Capsules and CsA resulted in reduced MPA exposure by 30-50% compared with patients receiving the combination of sirolimus and similar doses of Mycophenolate Mofetil 250 mg Capsules (see also section 4.4).

**Sevelamer:** decrease in MPA Cmax and AUC0-12 by 30% and 25%, respectively, were observed when Mycophenolate Mofetil 250 mg Capsules was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules 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 250 mg Capsules 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 250 mg Capsules.

**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 250mg Capsules 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 recipients initiated on Mycophenolate Mofetil 250 mg Capsules and tacrolimus, the AUC and Cmax of MPA, the active metabolite of Mycophenolate Mofetil 250 mg Capsules, 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 250 mg Capsules (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 250 mg Capsules (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 drug 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 250 mg Capsules therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules 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 250 mg Capsules in combination with other immunosuppressants during pregnancy. Cases of spontaneous absorption have been reported in patient exposed to Mycophenolate Mofetil 250 mg Capsules. 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 drug is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, Mycophenolate Mofetil 250 mg Capsules are 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 250 mg Capsules 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 250 mg Capsules, 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 250 mg Capsules (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 250 mg Capsules (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 250 mg Capsules 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, leucopoenia, anemia 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 250 mg Capsules 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 drug reactions, probably or possibly related to Mycophenolate Mofetil 250 mg Capsules, reported in ≥ 1/10 and in ≥ 1/100 to < 1/10 of patients treated with Mycophenolate Mofetil 250 mg Capsules 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 250 mg Capsules, reported in patients treated with Mycophenolate Mofetil 250 mg Capsules 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>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>
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<td>Common: Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteris, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis</td>
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<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Very common -</td>
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<tr>
<td></td>
<td>Common: Skin cancer, benign neoplasm of skin</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common: Leucopenia, thrombocytopenia, anaemia</td>
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<tr>
<td></td>
<td>Common: Pancytopenia, leucocytosis</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Common: Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hyperchlosterolaemia, hyperlipidaemia, hypophosphataemia, Hyperuricaemia, gout, anorexia</td>
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<td>Psychiatric disorders</td>
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<td>Common: Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia</td>
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<td>Common: Tachycardia</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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</table>

**Note:** 501 (2 g mycophenolate daily), 289 (3 g mycophenolate daily) and 277 (2 g IV / 3 g oral mycophenolate 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 250 mg Capsules 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.

Agranulocytosis (≥ 1/1,000 to < 1/100) and neutropenia has been reported; therefore regular monitoring of patients taking Mycophenolate Mofetil 250 mg Capsules is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with Mycophenolate Mofetil 250 mg Capsules, 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 250mg Capsules (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 250mg Capsules. 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 250mg Capsules.

**Congenital disorders:** see further details in section 4.6.

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

### 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 250 mg Capsules 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 250 mg Capsules 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 colestyramine (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 Cmax approximately 40 % lower compared to the late post-transplant period (3 – 6 months post-transplant).
Renal impairment:
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml•min^-1•1.73 m^-2) were 28 – 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3 – 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 250 mg Capsules 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 250 mg Capsules at a dose of 1 g bid in the early and late posttransplant 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 250 mg Capsules in the elderly has not been formally evaluated.

**Oral contraceptives:**

The pharmacokinetics of oral contraceptives were unaffected by coadministration of Mycophenolate Mofetil 250 mg Capsules (see also section 4.5). A study of the coadministration of Mycophenolate Mofetil 250 mg Capsules (1g 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 immuno suppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of Mycophenolate Mofetil 250 mg Capsules 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 Cmax) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or Cmax) 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 anophtalmia, 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 anophtalmia, 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 are 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 doses. 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 non-clinical 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

Excipients of Mycophenolate Mofetil 250mg Capsules are:

- Content of the capsules:
  - cellulose microcrystalline
  - hydroxy propyl cellulose
  - povidone K 90
  - croscarmellose sodium
talc
magnesium stearate
Capsule shells:
gelatin
sodium lauryl sulphate
potassium hydroxide
shellac
propylene glycol
indigo carmine (E132)
titanium dioxide (E171)
iron oxide red (E172)
iron oxide yellow (E172)
black iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Mycophenolate Mofetil 250 mg Capsules are available in blister pack of 20, 100, 300. The PVC/PVdC-aluminium blisters packed in final carton along with package insert. 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 250 mg Capsules should not be crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in Mycophenolate Mofetil 250 mg Capsules. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom
Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS
8 MARKETING AUTHORISATION NUMBER(S)
PL 17780/0323

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
18/11/2009

10 DATE OF REVISION OF THE TEXT
18/11/2009
MYCOPHENOLATE MOFETIL 250MG CAPSULES

Package leaflet: information for the user

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 get severe 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 capsules are used to prevent your body rejecting a transplanted kidney, heart or liver. Mycophenolate mofetil is used together with other medicines known as immunosuppressants.

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 have 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 problems, or have had 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 sunscreens with a high protection factor.

Taking with other medicines:
Please inform your doctor or pharmacist if you are taking/using other medicines or have recently taken/used other medicines, even if these were obtained without a prescription.

If the answer to any of the following questions is “yes”, talk to your doctor before you start to take mycophenolate mofetil:
• Are you taking medicines that contain azathioprine or other immunosuppressant substances (which are sometimes given to patients after an organ transplant), or any medicines for the treatment of patients with high blood cholesterol, antinesi (antihistamines), aspirin, or phosphates binders (used in patients with chronic renal failure) to reduce the absorption of phosphates or any other medicines (including those you can buy without a prescription), that your doctor does not know about?
• Do you need vaccinations (live vaccines)?
Your doctor will advise you which vaccination is suitable for you.

Taking mycophenolate mofetil with food and drink:
Food and drink do not affect 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, while taking mycophenolate mofetil, and for 6 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 use machines.

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.

Mycophenolate mofetil is usually taken as follows:

Renal transplant (kidney):
Adults:
The first dose will be given within 72 hours after the transplant operation. The recommended daily dose is 8 capsules (2 g of the active ingredient), taken as 2 separate doses. This means taking 4 capsules in the morning and then 4 capsules 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/kg taken twice daily.

Heart transplant:
Adults:
The first dose will be given within 7 days following the transplant operation.

The recommended daily dose is 12 capsules (3 g of the active ingredient), taken as 2 separate doses. This means taking 6 capsules in the morning and 6 capsules 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 12 capsules (3 g of the active ingredient), taken as 2 separate doses. This means taking 6 capsules in the morning and 6 capsules in the evening.

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

Method of administration:
Swallow your capsules whole with a glass of water.

• Do not break or crush them and do not take any capsules that have broken open or split. Avoid contact with any powder that spills out from damaged capsules. If a capsule breaks open accidentally, wash any powder from your skin with soap and water. If any powder gets into your eyes or mouth, rinse thoroughly with plenty of plain, fresh water.

• The treatment will continue for so long as you need immunosuppression to prevent your transplanted organ from being rejected.

If you take more mycophenolate mofetil than you should:
If you take more capsules than you should or if someone else has accidentally taken your capsules, consult a doctor immediately or go to the hospital straight away.

If you forget to take mycophenolate mofetil:
If you have forgotten to take your medicine take it as soon as you remember. Then continue to take it at the usual times.

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.

Some of the more usual problems are dryness, brown white spots and red spots in your blood, infection and vomiting. Your doctor will do regular blood tests to monitor any changes in the levels of any
of the substances carried in your blood, e.g. sugar, fat, cholesterol. Children may be more likely than adults to have side effects such as diarrhoea, irregular periods, lower white blood cells and fewer red cells in the blood.

Mycophenolate mofetil reduces your body's own defence mechanisms to stop you rejecting your transplanted kidney, heart, or liver. Consequently, your body will not be as good at normal fighting infections. So if you are taking Mycophenolate mofetil you may therefore catch more infections than usual, such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract. As can happen in patients taking this type of medicine, a very small number of Mycophenolate mofetil patients have developed cancer of the lymphoid tissues and skin.

General unwanted effects affecting your body as a whole could include hypersensitivity (such as anaphylaxis, angioedema), fever, malaise, difficulty in sleeping, pain (such as abdominal, chest, pleuritic, pain on passing urine), headache, flu symptoms and swelling.

Other unwanted effects may include:

- Disorders of the skin such as acne, cold sores, tingling, skin growth, hair loss, rash, itching.
- Urinary disorders such as kidney problems or the urgent need to pass urine.
- Disorders of the digestive system and mouth such as constipation, nausea, indigestion, pancreas inflammation, intestinal disorders including bleeding, inflammation of the stomach, liver problems, inflammation of the colon, loss of appetite, feeling sick, swelling of the mouth and mouth ulcers.
- Disorders of the nervous and sense organs such as convulsions, tension, dizziness, depression, diarrhoea, numbness, muscle pains, anxiety, changes in thinking or mood.
- Metabolic, blood and vascular disorders such as weight loss, gain, high blood sugar, swelling, cramps and bruises, change in blood pressure, abnormal heartbeat and dilation of blood vessels may be seen.
- Disorders of the lungs such as pneumonia, bronchitis, shortness of breath, cough, fluid in the lungs/heart cavity, sputum problems.
- Any of the side effects gets worse, 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 without 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 capsules after the expiry date (see leaflet).
- Do not store above 30°C. Store in the original package in order to protect from moisture.
- Medicines should not be disposed of via waste water or in the household waste. Ask your pharmacist how to dispose of medicines that are no longer required. These measures will help protect the environment.

5. FURTHER INFORMATION

What Mycophenolate Mofetil 250 mg Capsules contain
- The active substance is mycophenolate mofetil.
- The other ingredients of Mycophenolate Mofetil 250 mg Capsules are:
- Content of the capsules:
- colophonum microcrystalline, hydroxypropylcellulose, povidone K-90, croscarmellose sodium, talc, magnesium stearate.
- Capsule shells:
- gelatin, calcium hydroxide, polvahan sodium hydroxide, shellac, propylene glycol, ethyl carbitol, ethyl alcohol, water, iron oxide yellow (E172), iron oxide red (E172), black iron oxide (E172).
Module 4

Labelling

Blister:
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mycophenolate Mofetil 250mg Capsules, in the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants, is approvable.

EXECUTIVE SUMMARY

Problem statement
This decentralised application concerns a generic version of mycophenolate mofetil, submitted under Article 10.1.

The originator product is CellCept 250 mg capsules by Roche Registration Ltd, registered via a Centralised Procedure in the EU since 14 February 1996.

With the UK as the Reference Member State in this Decentralised Procedure, Winthrop Pharmaceuticals Ltd is applying for a marketing authorisation for Mycophenolate Mofetil 250mg Capsules in France, Spain and Germany.

About the product
Mycophenolate mofetil belongs to the immunosuppressant group. Its active metabolite, mycophenolate acid, is a potent inhibitor of guanosine nucleotide synthesis. Due to its potent cytostatic effect on lymphocytes the proposed indication is in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

The proposed indication is:

Mycophenolate Mofetil 250 mg capsules are indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

As the proposed indication and posology are identical to the reference product, they are satisfactory.

General comments on the submitted dossier
The dossier is considered adequate.

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 these product types at all sites responsible for the manufacture and assembly of this product. 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. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The submitted clinical bioequivalence study was conducted in line with GCP.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**
The chemical-pharmaceutical documentation and Expert Report in relation to Mycophenolate Mofetil 250mg Capsules are of sufficient quality in view of the present European regulatory requirements. The active 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 with the drug substance. No significant changes in any parameters were observed and the results support the proposed re-test period.

**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. Validations of the analytical methods have been presented. Batch analysis results show that the finished products meet 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. The stability data support the proposed shelf-life of 24 months with the storage precaution “Store below 30°C. Store in the original package in order to protect from moisture.”

**Non clinical aspects**
The pharmacological, pharmacokinetic and toxicological properties of mycophenolate mofetil are well known. As mycophenolate mofetil is a well known active 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 expert who has a medical degree. The overview, dated November 2007, refers to 58 references from the published literature dated up to 2007. The overview is considered to be 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 250mg Capsules from a non-clinical point of view.
Clinical aspects

Pharmacokinetics
Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract. It undergoes presystemic metabolism to form active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen between 6 and 12 hours after dosing. MPA is metabolised by glucuronidation to the inactive mycophenolic acid, glucuronide. The majority of a dose is excreted in the urine as glucuronide, about 6% is recovered in faeces. MPA is 97% bound to plasma albumin. The mean half-life of MPA after an oral dose of mycophenolate mofetil has been reported to be 17.9 hours.

The applicant has conducted a bioequivalence study in order to confirm that the product Mycophenolate 250 mg capsules is bioequivalent to the reference product.

Bioequivalence study

Study design
This was an open-label, randomised, two-treatment, two-period, two sequence crossover bioavailability and bioequivalence study conducted in healthy adult human male subjects under fasting conditions.

A single dose of the investigational products (one capsule of 250 mg) was administered orally to each subject in each period with 240 ml of water while in sitting position after an overnight fast of at least 10 hours. A washout period of 11 days was maintained between the two dosing days in each group.

Serial blood sampling before dosing and at 0.083, 0.167, 0.25, 0.333, 0.50, 0.66, 0.83, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, 24, 48 and 60 hours after drug administration was carried out in each group. Mycophenolate mofetil and mycophenolic acid (MPA) in plasma were quantified by a validated LC-MS/MS method. Although this was an open label study, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the test and reference products.

Blood sampling and washout period are adequate. As co-administration of food is known to have no effect on AUC but only on Cmax in renal transplant patients the administration of study drugs under fasting conditions is also satisfactory. The choice of a single dose 250 mg capsule study is justified as this application concerns an immediate release formulation and it is well known that the most sensitive way of comparing the bioequivalence of two formulations is by testing one unit of the test drug with that of the reference.

Test and reference products
Test: Mycophenolate mofetil 250 mg Capsules
Reference: CellCept 250 mg capsules by Roche Registration Ltd
Population(s) studied
Fifty-four healthy male subjects aged between 18 and 55 years were enrolled in the study, out of which two subjects were checked in to account for possible dropouts prior to dosing in period I.

Fifty-two subjects were dosed in period I and 50 subjects completed the trial.

Two subjects were withdrawn on medical grounds. Both withdrawals were considered to be due to medical adverse events unlikely to be related to the study drug.

Analytical methods
Mycophenolate mofetil and mycophenolate acid (MPA) in plasma were quantified by a validated LC-MS/MS method.

Pharmacokinetic Variables
The following variables were analysed:

$T_{max}$, $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $\lambda_z$, $t_{1/2}$ and $AUC\%_{Extrap-obs}$.

Statistical methods
Descriptive statistics were reported for mycophenolate mofetil and MPA.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for un-transformed and ln-transformed PK parameters, $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were computed for MPA.

The 90% parametric CI was calculated for un-transformed and ln-transformed $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for MPA. Bioequivalence between the test and reference products was concluded if 90% CI fell within 80-125% for ln-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ for MPA and 90% CI fell within 75-133% for ln-transformed $C_{max}$ for MPA.

As mycophenolate mofetil undergoes rapid and complete metabolism to the active metabolite MPA, an adequate plasma concentration of mycophenolate mofetil may not be obtained. Therefore, the choice of selecting MPA data for confirmation of bioequivalence between test and reference products and providing data on mycophenolate mofetil as supportive evidence is adequate. The applicant has justified widening the CI for $C_{max}$ to 75-133% as it is reported in the literature that mycophenolate mofetil shows a high intrasubject variability of greater or equal 30%

Results
**Table-A: Descriptive Statistics of Formulation Means for Mycophenolate mofetil (n=50)**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product-A</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (h)</strong></td>
<td>0.500</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng / mL)</strong></td>
<td>2.400 ± 2.3119</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-4h&lt;/sub&gt; (ng.h / mL)</strong></td>
<td>1.393 ± 0.9269</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h / mL)</strong></td>
<td>1.554 ± 1.0306&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>λ&lt;sub&gt;e&lt;/sub&gt; (1 / h)</strong></td>
<td>1.368 ± 0.7836&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>t½ (h)</strong></td>
<td>0.709 ± 0.5948&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;%&lt;/sub&gt; Extrap_obs (%)</strong></td>
<td>9.463 ± 4.0305&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*<sup>T<sub>max</sub> is represented in median value, #: n=48, ^: n=45</sup>  

**Note:** AUC<sub>%</sub> Extrap_obs (%) was > 20% for two subjects in reference and five subjects in test. Hence, the number of subjects used for computation of AUC<sub>0-∞</sub>, λ<sub>e</sub>, t½ and AUC<sub>%</sub> Extrap_obs (%) were 48 and 45 for reference and test formulations respectively.

**Table-B: Descriptive Statistics of Formulation Means for mycophenolic acid (n=50)**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product-A</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (h)</strong></td>
<td>0.500</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng / mL)</strong></td>
<td>10802.000 ± 3750.7806</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-4h&lt;/sub&gt; (ng.h / mL)</strong></td>
<td>12653.346 ± 4235.0853</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h / mL)</strong></td>
<td>13420.736 ± 4467.6524</td>
</tr>
<tr>
<td><strong>λ&lt;sub&gt;e&lt;/sub&gt; (1 / h)</strong></td>
<td>0.111 ± 0.0585</td>
</tr>
<tr>
<td><strong>t½ (h)</strong></td>
<td>8.404 ± 4.6964</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;%&lt;/sub&gt; Extrap_obs (%)</strong></td>
<td>5.708 ± 2.7755</td>
</tr>
</tbody>
</table>

*<sup>T<sub>max</sub> is represented in median value</sup>
Mycophenolate mofetil and MPA were not detected at predose levels, indicating washout period was satisfactory. The results of the study showed that the test product and reference product are bioequivalent as the MPA confidence intervals for both Cmax and AUC fall within the acceptance criteria ranges of 80-125% in line with current guidelines.

Safety
There were 10 adverse events (AE) and two medical events reported by eight subjects. All of the events were mild in nature and were resolved. Two significant AE were reported by two subjects but the relation to the investigational products was considered unlikely. No deaths or serious AE were reported during the study.

Pharmacokinetic conclusion
The submitted bioequivalence study has confirmed that the applicant’s medicinal product is bioequivalent to the reference product with respect to the rate and extent of absorption.

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

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

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

Pharmacovigilance system

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>10338.537</td>
<td>10165.717</td>
</tr>
<tr>
<td>AUC_{0-4} (ng.h/mL)</td>
<td>12185.159</td>
<td>11999.868</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng.h/mL)</td>
<td>12884.070</td>
<td>12731.732</td>
</tr>
</tbody>
</table>
The Applicant has provided a satisfactory description of the Pharmacovigilance system.

**Risk Management Plan**
No safety concerns requiring additional risk minimization activities have been identified with the reference product. A detailed RMP is not considered necessary for this generic application.

**Assessment of User Testing**
User testing-evaluation is bridged to the authorised and user-tested mycophenolate mofetil 500mg tablet product granted via UK/1111/001/DC. This is accepted as the parent and daughter PIL are practically identical and the differences are only minor. An adequate bridging report has been submitted by the applicant.

**BENEFIT RISK ASSESSMENT**
The benefit-risk ratio is considered favourable.