Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Mycophenolate Lek 250mg Capsules

UK/H/1037/001/DC
UK licence no: PL 16220/0005

Lek Pharmaceuticals d.d.

LAY SUMMARY

The MHRA has granted Lek Pharmaceuticals d.d. a Marketing Authorisation (licence) for the medicinal product Mycophenolate Lek 250mg Capsules. This is a prescription-only medicine (POM) that is used together with other drugs, known as ciclosporins and corticosteroids, to prevent the body rejecting a transplanted kidney, heart or liver.

Mycophenolate mofetil belongs to a group of drugs known as immunosuppressants.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Mycophenolate Lek 250mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Mycophenolate Lek 250mg Capsules
Type of Application	Generic, Article 10.1
Active Substance	Mycophenolate mofetil
Form	Capsules
Strength	250mg
MA Holder	Lek Pharmaceuticals d.d, Verovškova 57, 1526 Ljubljana, Slovenia
RMS	UK
CMS	Poland, Slovenia
Procedure Number	UK/H/1037/001/DC
Timetable	Day 210 – 18th February 2008

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mycophenolate Lek 250 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of mycophenolate mofetil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Hard gelatin capsules (size 1) with blue opaque cap and orange opaque body.

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 1.0 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/m^2 administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate mofetil should only be prescribed to patients with a body surface area of at least 1.25 m^2. Patients with a body surface area of 1.25 to 1.5 m^2 may be prescribed mycophenolate mofetil at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area greater than 1.5 m^2 may be prescribed mycophenolate mofetil 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 pediatric cardiac transplant patients.

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

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 to the active substance or to any of the excipients.
Mycophenolate mofetil is contraindicated in women who are breast-feeding (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, 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 minimize 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 should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Oversuppression of the immune system increases the susceptibility to infection including opportunistic infections, fatal infections and sepsis (see section 4.8).

Patients receiving mycophenolate should be monitored for neutropenia, which may be related to mycophenolate itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < $1.3 \times 10^3/\mu l$) it may be appropriate to interrupt or discontinue mycophenolate.

Patients should be advised that during treatment with mycophenolate 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 has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation, mycophenolate should be administered with caution in patients with active serious digestive system disease.

Mycophenolate 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.

It is recommended that mycophenolate 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 with medicinal products that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of mycophenolate.

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

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir: higher MPAG (mycophenolic acid glucuronide) and 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 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 (three times a day) 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.

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.

Ciclosporin A: ciclosporin A pharmacokinetics were unaffected by mycophenolate mofetil.

Several studies have demonstrated that ciclosporin A reduces MPA plasma AUC levels by 19 - 38 %, possibly as a result of inhibiting biliary secretion with consequent reduction of the entero-hepatic recirculation. However, as efficacy studies were carried out using mycophenolate combined with ciclosporin A and corticosteroids, these findings do not affect the recommended dose requirements (see section 4.2).

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 (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 dose adjustment is not required. In patients with renal impairment in which mycophenolate and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Oral contraceptives: the pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by coadministration of mycophenolate (see also section 5.2).

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

Tacrolimus: *in renal transplant patients*: stable renal transplant patients receiving ciclosporin and mycophenolate (1 g BID) showed about a 30 % increase in MPA plasma AUC and about a 20 % decrease in MPAG plasma AUC when ciclosporin was replaced with tacrolimus. MPA C_{max} was not affected, while MPAG C_{max} was reduced by approximately 20 %. The mechanism of this finding is not well understood. Increased biliary secretion of MPAG accompanied with increased enterohepatic recirculation of MPA may be partly responsible for the finding, since the elevation of MPA concentrations associated with tacrolimus administration was more pronounced in the later portions of the concentration-time profile (4 – 12 hours after dosing). In another study in renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by mycophenolate.

In hepatic transplant patients: very limited pharmacokinetic data on MPA AUC are available in hepatic transplant patients treated with mycophenolate in combination with tacrolimus. In a study designed to evaluate the effect of mycophenolate on the pharmacokinetics of tacrolimus in stable hepatic transplant patients, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate (1.5 g BID) were administered to patients taking tacrolimus.

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 section 4.4).

4.6 Pregnancy and lactation

It is recommended that mycophenolate therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning mycophenolate 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 is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. Mycophenolate 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 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 in combination with other immunosuppressants during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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 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/m^2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric

population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

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

Other adverse reactions:
Adverse reactions, probably or possibly related to mycophenolate mofetil, reported in ≥10 % and in 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 heading of frequency, using the following categories:
Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1,000); Very rare (<1/10,000), including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

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

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

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

Gastrointestinal: 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, infectious endocarditis, tuberculosis and atypical mycobacterial infection. Agranulocytosis(≥1/1000 to

<1/100)and neutropenia have been reported in some patients, 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.

Hypersensitivity: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported.

Congenital disorders: see further details in section 4.6.

4.9 Overdose

The experience with overdose of mycophenolate mofetil in humans is very limited. The events received from reports of overdose fall within the known safety profile of the medicinal product.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressant, ATC code: LO4AA06.

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 is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40 % in the presence of food.

Mycophenolate mofetil is not measurable systemically in plasma following oral administration. MPA at clinically relevant concentrations, is 97 % bound to plasma albumin.

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of 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 C_{max} approximately 40 % lower compared to the late post-transplant period (3 – 6 months post-transplant).

Renal impairment:
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate <25 ml/min/1.73 m^2) were 28 – 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3 – 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function:
In patients with delayed renal graft function post-transplant, mean MPA AUC (0–12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate 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/m^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate 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 posttransplant period.

Elderly patients (≥ 65 years):
Pharmacokinetic behavior of mycophenolate in the elderly has not been formally evaluated.

Oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by coadministration of mycophenolate (see also section 4.5). A study of the coadministration of mycophenolate (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 on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

5.3 Preclinical safety data

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

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

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day.

The systemic exposure at this dose represents 2 to 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 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 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

Capsule content:
Maize starch, pregelatinised
Croscarmellose sodium
Povidone (K-90F)
Magnesium stearate

Capsule shell:
Gelatine
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PE/PVDC//Aluminium blisters: 3 years.
HDPE container: 3 years; after first opening: use within 2 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC//Aluminium blister: 100 and 300 capsules
HDPE container: 250 capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, the capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in the 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

Lek Pharmaceuticals d.d.
Verovškova 57
1526 Ljubljana
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

PL 16220/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2008

10 DATE OF REVISION OF THE TEXT

15/09/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

Package leaflet: Information for the user

SZ00000LT000

Mycophenolate Lek 250 mg Capsules

Mycophenolate mofetil

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

In this leaflet:

1 What Mycophenolate Lek 250 mg Capsules are and what they are used for

Mycophenolate mofetil belongs to the class of drugs known as immunosuppressants.
Mycophenolate Lek 250 mg Capsules are used to prevent your body rejecting a transplanted kidney, heart or liver.
Mycophenolate Lek 250 mg Capsules are used together with other drugs known as ciclosporin and corticosteroids.

2 Before you take Mycophenolate Lek 250 mg Capsules

Do not take Mycophenolate Lek 250 mg Capsules:
- If you are allergic (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of Mycophenolate Lek 250 mg Capsules.
- If you are breast-feeding.

Take special care with Mycophenolate Lek 250 mg Capsules
- Tell your doctor if you have, or ever have had any problems with your digestive system, e.g. stomach ulcers.
- Tell your doctor if you suffer from an enzyme defect called 'Lesch-Nyhan syndrome' or 'Kelley Seegmiller syndrome'.
- Limit your exposure to sunlight and UV light by wearing appropriate protective clothing and using a sunscreen with a high protection factor. There is an increased risk of skin cancer because mycophenolate reduces your body's defense mechanism.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Take care with the following medicines:
- Azathioprine or tacrolimus or other immunosuppressive agents (which are sometimes given to patients after a transplant operation),
- Colestyramine (used to treat patients with high blood cholesterol),
- Antacids (for heartburn)
- Aciclovir, ganciclovir (for viral infections)
- Live vaccines should be avoided. Your doctor will have to advise you what is indicated for you.

Pregnancy and breast-feeding:
Do not take any mycophenolate if you are breast-feeding. You must not use mycophenolate 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 6 weeks after you have stopped taking mycophenolate mofetil. This is because mycophenolate may cause damage, including problems with development of the ears, to your unborn baby. Tell your doctor straight away if you are breast-feeding, become pregnant or plan to start a family in the near future.
Ask your doctor for advice before taking any medicine.

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

3 How to take Mycophenolate Lek 250 mg Capsules

Always take Mycophenolate Lek 250 mg Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is as follows:

Kidney Transplant

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 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/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 12 capsules (3 g of the active ingredient) taken as 2 separate doses. This means taking 6 capsules in the morning then 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 then 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 and route 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.

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

If you take more Mycophenolate Lek 250 mg Capsules than you should:
If you take more capsules than you have been told to take, or if someone else accidentally takes your medicine, immediately see a doctor or go to a hospital straight away.

If you forget to take Mycophenolate Lek 250 mg Capsules:
Do not worry, take it as soon as you remember.
If it is almost time to take the next dose, wait until then and continue with your usual schedule.

Do not double the dose to make up for the one missed.

If you stop taking Mycophenolate Lek 250 mg Capsules:
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 or pharmacist.

Please turn over

4 Possible side effects

Like all medicines, Mycophenolate Lek 250 mg Capsules can cause side effects, although not everybody gets them.

Serious side effects
If you notice one of the following serious side effects, talk to your doctor or go to a hospital immediately:
Following serious side-effects are **common** (affect less than 1 out of 10 people):
- In case of any evidence of infection (e.g. fever, sore throat), un expected bruising and/or bleeding
- Unusual bruising or bleeding, includes vomiting blood or passing blood in your stools
- Fits (convulsions)
- Yellowing of the skin and eyes, unusual tiredness or fever, dark coloured urine (signs of inflamed liver).

Following serious side-effects are **very rare** (affect less than 1 out of 10,000 people):
- Hypersensitivity reactions (anaphylaxis, angioedema): If you develop a swelling of the eyelids, face, lips, mouth or tongue, start to itch or have difficulty in breathing or swallowing, or extreme dizziness

Other possible side-effects
Elderly patients may generally be at increased risk of side effects.
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.

Following side-effects are very common (affect more than 1 out of 10 people):
- Fewer white cells and/or red cells or platelets in your blood. Your doctor will do regular blood tests to monitor any changes in the number of your blood cells or changes in the levels of any of the substances carried in your blood, e.g. sugar, fat, cholesterol
- Diarrhoea, feeling or being sick, abdominal pain
- Cold sores, shingles
- Urinary tract infections, urgent need to pass urine

Following side-effects are common (affect less than 1 out of 10 people):
- **Infections of the skin, mouth, stomach and intestines, and lungs:** 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 as normal at fighting infections. So if you are taking mycophenolate mofetil you may therefore catch more infections than usual.
- 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.**
- **Infections,** such as flu symptoms, vaginal thrush
- **Metabolic and nutrition disorders,** such as weight loss, loss of appetite, gout, high blood sugar, high blood fat and cholesterol
- **Blood, cardiac and vascular disorders** such as bleeding, clots and bruises, increased level of white blood cells, change in blood pressure, abnormal heart beat and dilatation of blood vessels
- **Nervous system and psychiatric disorders** such as convulsions, tremor, dizziness, numbness, muscle spasms, headache, anxiety, depression, confusion, agitation, drowsiness, changes in thinking or mood, insomnia
- **Respiratory and thoracic disorders** such as pneumonia, bronchitis, shortness of breath, cough, fluid on the lungs/chest cavity, sinus problems, rhinitis, (runny or blocked nose), pharyngitis
- **Gastrointestinal disorders** such as constipation, indigestion, pancreas inflammation, intestinal disorders including bleeding, inflammation of the stomach or oesophagus, gastric ulcer, duodenal ulcer, liver problems, inflammation of the colon, inflammation of the abdominal cavity, flatulence, mouth ulcers and impaired taste
- **Skin disorders** such as acne, skin growth, hair loss, rash, itching
- **Renal and urinary disorders** such as kidney problems
- **General disorders** such as fever, chills, malaise, weakness, pain (such as chest, joint/muscle), and swelling

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. However, do not stop taking your medicine unless you have discussed this with your doctor first.

5 How to store Mycophenolate Lek 250 mg Capsules

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the carton, on the blister or on the container after EXP. The expiry date refers to the last day of that month.
After first opening of the container: use within 2 months.

This medicinal product does not require any special storage conditions.

Medicines should be 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 Lek 250 mg Capsules contain
- The active substance is mycophenolate mofetil. Each capsule contains 250 mg of mycophenolate mofetil.
- The other ingredients in the capsule content are pregelatinised maize starch, croscarmellose sodium, povidone (K-90F), magnesium stearate. The capsule shell consists of gelatine, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), indigo carmine (E132).

What Mycophenolate Lek 250 mg Capsules look like and contents of the pack
Hard gelatin capsules (size 1) with blue opaque cap and orange opaque body.
PVC/PE/PVDC//Aluminium blister: 100 and 300 capsules.
HDPE container: 250 capsules.

Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer

Marketing authorization holder:
Lek Pharmaceuticals d.d.
Verovškova 57
1526 Ljubljana
Slovenia

Manufacturer
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Barleben
Germany

or

LEK S.A.
Ul. Podlipie 16
95 010 Stryków
Poland

or

LEK S.A.
ul. Domaniewska 50 C,
02-672 Warsaw
Poland

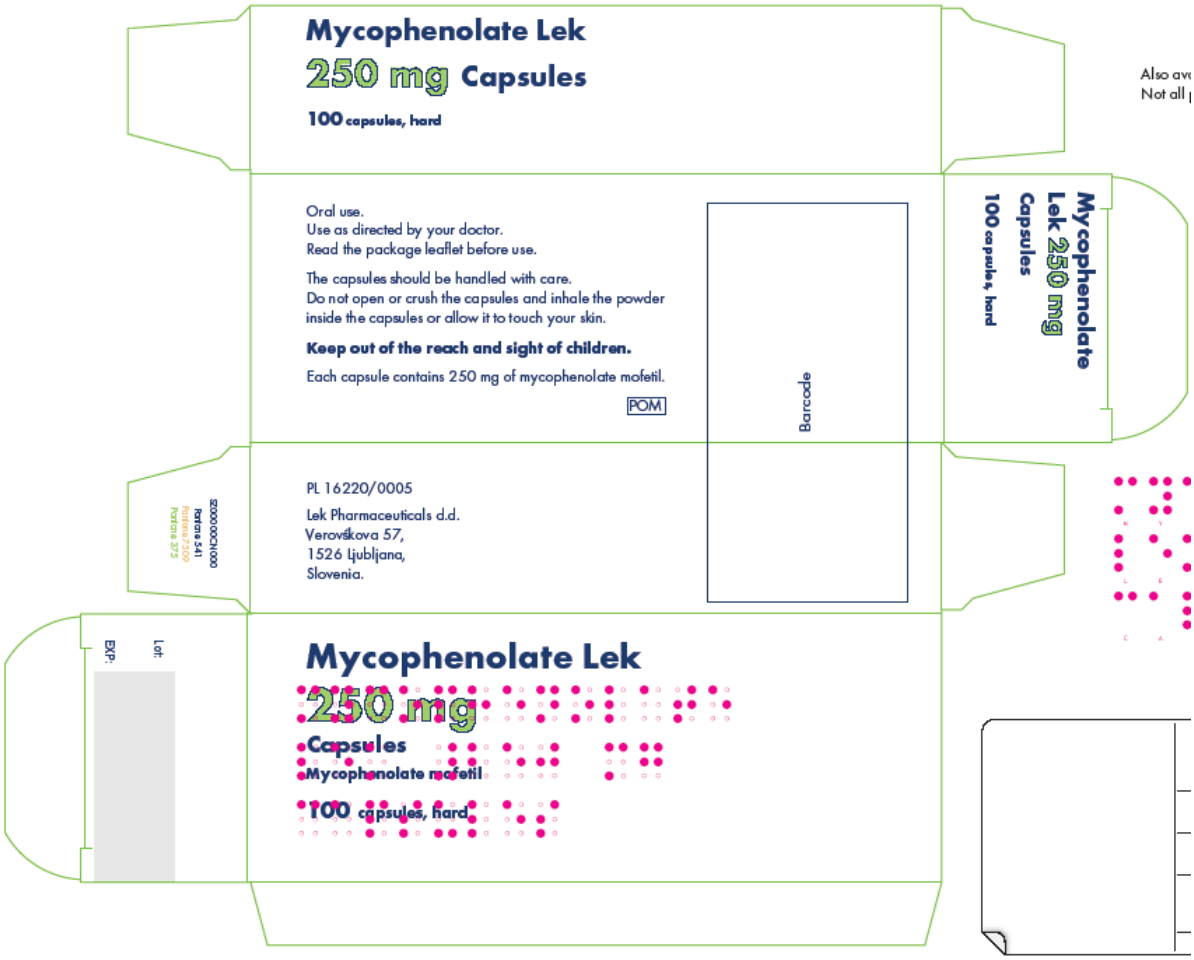
This medicinal product is authorised in the Member States of the EEA under the following names:

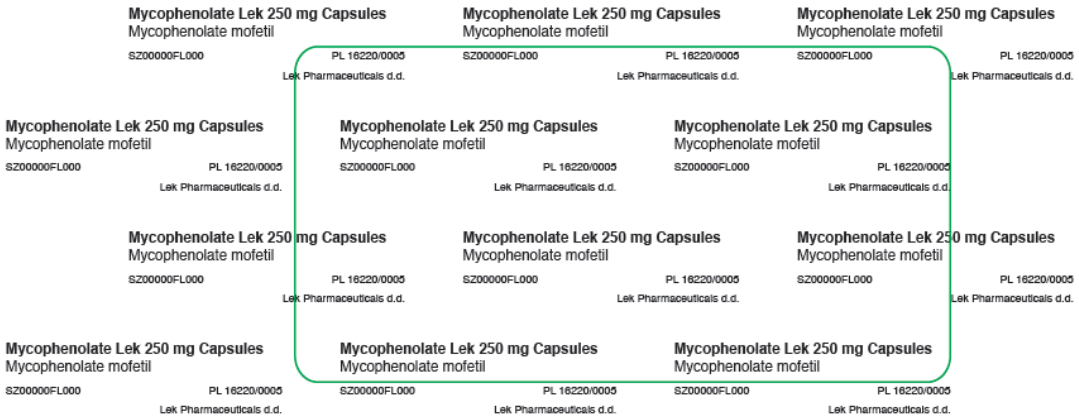
United Kingdom:	Mycophenolate Lek 250 mg Capsule
Poland:	Mycophenolate Lek 250 mg Kapsulki
Slovenia:	Mycofenolat Lek 250 mg Kapsule

This leaflet is last approved in 04/2008 *(to be amended after approval)*

SZ00000LT000

Module 4
Labelling





Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK, Poland and Slovenia have granted marketing authorisations for Mycophenolate Lek 250mg Capsules to Lek Pharmaceuticals d.d, for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

This is an application made under Article 10.1 of 2001/83 EC, as amended, for Mycophenolate Lek 250mg Capsules, claiming to be a generic medicine to CellCept 250mg Capsules (Roche Registration Ltd UK), which was granted a marketing authorisation in the UK on 14th February 1996, thus fulfilling the 10-year rule.

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 allogenic renal, cardiac or hepatic transplants.

No new preclinical studies were conducted, which is acceptable given that the application was a generic of a product that has been licensed for over 10 years.

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

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Mycophenolate Lek 250mg Capsules
Name(s) of the active substance(s) (INN)	Mycophenolate mofetil
Pharmacotherapeutic classification (ATC code)	Immunosuppressive agent (LO4AA06)
Pharmaceutical form and strength(s)	250mg Capsules
Reference numbers for the Decentralised Procedure	UK/H/1037/001/DC
Reference Member State	United Kingdom
Member States concerned	Poland and Slovenia
Marketing Authorisation Number(s)	PL 16220/0005
Name and address of the authorisation holder	Lek Pharmaceuticals d.d, Verovškova 57, 1526 Ljubljana, Slovenia

III SCIENTIFIC OVERVIEW AND DISCUSSION

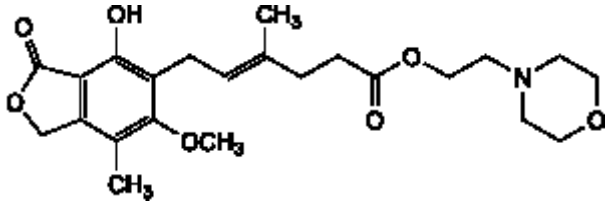
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Mycophenolate mofetil

Chemical name: i. 2-(morpholin-4-yl)ethyl-(4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl-4-methylhex-4-enoate
ii. mycophenolic acid 2-(4-morpholinyl)ethyl ester

Structure:



Physical form: White to off-white or almost white, crystalline powder. Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

Molecular formula: $C_{23}H_{31}NO_7$

Molecular weight: 433.5

Mycophenolate mofetil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of active mycophenolate mofetil are covered by a certificate of suitability.

Active mycophenolate mofetil is stored in an airtight polyethylene bag, which is contained in polyester/aluminium/polyethylene bags.

An adequate retest period has been defined based on conducted stability studies.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients in the capsules contents (pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate) and the capsule shell (gelatin, red iron oxide [E172], yellow iron oxide [E172], titanium dioxide [E171] and indigocarmine [E132]).

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of red iron oxide, yellow iron oxide and indigo carmine (which comply with suitable in-house specifications and 95/45/EEC). Satisfactory certificates of analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients used contain materials of animal or human origin. Current TSE Certificates of Suitability have been provided from all suppliers of gelatin to show that it is produced in-line with current guidelines concerning the minimising of transmission of BSE/TSE.

Product development

The applicant has provided a suitable product development section. Dissolution data and impurity profiles support the pharmaceutical equivalence of the proposed product with the reference product CellCept 250mg Capsules.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the finished product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Satisfactory certificates of analysis have been provided for all working standards used.

Container Closure System
The primary packaging is:
(i) a polyvinylidene chloride / polyvinylchloride / polyethyelene / aluminium blister, which is stored in a cardboard container in pack sizes of 100 and 300 capsules.
(ii) a high-density polyethylene container with a polypropylene closure containing 250 capsules.

Specifications and certificates of analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for both packaging types (although the shelf-life changes to 2 months after opening for the high-density polyethylene container).

Bioequivalence
See Clinical Assessment.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is pharmaceutically satisfactory.

Summary of Product Characteristics (SPC)
The SPC is consistent with that for the reference product and is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory

Patient Information Leaflet
This is consistent with that for the reference products and is pharmaceutically satisfactory. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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 it contains.

MAA Forms
These are pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products. In addition, similar dissolution and impurity profiles have been demonstrated for the proposed and reference products.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, 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 not provided any.

A preclinical expert report has been written by suitably qualified persons and is satisfactory.

III.3 CLINICAL ASPECTS
Pharmacokinetics
Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract. It undergoes presystemic metabolism to active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen at between 6 to 12 hours after a dose. 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 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 proposed product (Mycophenolate 250mg Capsules) can be considered a generic medicinal product of the reference product (CellCept 250mg Capsules).

Bioequivalence study
This was an open-label, randomised, two-treatment, two-period, two sequence, crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions, comparing Mycophenolate 250mg Capsules (Test Product) versus CellCept 250mg Capsules (Reference Product).

A single dose of the investigational products was administered orally to each subject in each period with 240 ml of water while in a sitting position, after an overnight fast of at least 10 hours. The subjects were not allowed to lie down for 3 hours after dosing. A washout period of 7 days was maintained between the two dosing days in each group. The plasma samples were analysed for all subjects that completed the trial successfully.

Serial blood sampling before dosing and up to 48 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.

T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and half-life were calculated independently for mycophenolate mofetil and MPA by employing a non-compartmental model. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range for ln-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ for MPA.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for untransformed and ln-transformed PK parameters, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ were computed for MPA. Only descriptive statistics were reported for mycophenolate mofetil.

The results for MPA are presented below:

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	9882.339	10397.387	105.2%	97.46-113.58
AUC_{0-t} (ng.h/ml)	12486.041	13179.002	105.5%	102.59-108.59
$AUC_{0-\infty}$(ng.h/ml)	13626.591	14466.647	106.2%	102.65-109.80

No serious or significant adverse events were reported during the study.

Conclusion

The study design is appropriate and the results showed that the test and reference products are bioequivalent as the 90% CI for C_{max} and AUC fall within the acceptance range of 80-125%, in-line with current guidelines.

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. As 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.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Mycophenolate Lek 250mg Capsules 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.

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

Bioequivalence has been demonstrated between the applicant's Mycophenolate 250mg Capsules and CellCept 250mg Capsules.

No new or unexpected safety concerns arise from this application.

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

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. 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

Date submitted	Application type	Scope	Outcome