COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mycofenolaat Mofetil Accord 500 mg film-coated tablets
(mycofenolate mofetil)

NL/H/4839/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Mycofenolaat Mofetil Accord 500 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/1055/001/DC). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Mycophenolate Mofetil 500mg Film Coated Tablets

UK/H/1055/001/DC
UK licence no: PL 20075/0001

Accord Healthcare Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Mycophenolate Mofetil 500mg Film Coated Tablets. This medicine is available on prescription only.

Mycophenolate Mofetil 500mg Film Coated Tablets is used together with other drugs, known as ciclosporins and corticosteroids, to prevent the body rejecting a translanted kidnesy, heart or liver.

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

The test product was considered the same as the original product CellCept 500mg Tablets (Roche Registration Ltd) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Mycophenolate mofetil 500mg Film Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Mycophenolate Mofetil 500mg Film Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Mycophenolate Mofetil
Form	Film-Coated Tablet
Strength	500mg
MA Holder	Accord Healthcare Limited
RMS	UK
CMS	Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Portugal, Sweden, Slovenia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland Slovak Republic and Romania
Procedure Number	UK/H/1055/001/DC
Timetable	Day 210 – 17/11/2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil 500 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Mycophenolate Mofetil 500 mg.
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
Purple colored, capsule shaped, biconvex, film coated tablet debossed 'AHI' on one side and '500' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with Mycophenolate Mofetil should be initiated and maintained by appropriately qualified transplant specialists.
Use in renal transplant:
Adults: Oral Mycophenolate Mofetil should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).
Children and adolescents (aged 2 to 18 years): The recommended dose of Mycophenolate Mofetil is 600 mg/m^2 administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate Mofetil 500 mg Tablets should only be prescribed to patients with a body surface area greater than 1.5 m^2, at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.
Children (< 2 years): There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.
Use in cardiac transplant:
Adults: Oral Mycophenolate Mofetil should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).
Children: No data are available for paediatric cardiac transplant patients.
Use in hepatic transplant:
Adults: IV Mycophenolate Mofetil should be administered for the first 4 days following hepatic transplant, with oral Mycophenolate Mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).
Children: No data are available for paediatric hepatic transplant patients.
Use in elderly (≥ 65 years): The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.
Use in renal impairment: In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 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 mycophenolate mofetil or to any of the excipients have been observed (see Section 4.8). Therefore, Mycophenolate Mofetil is contraindicated in patients with a hypersensitivity to Mycophenolate Mofetil or Mycophenolic acid or any of the excipients.
Mycophenolate Mofetil is contraindicated in women who are breastfeeding (see section 4.6).
For information on use in pregnancy and contraceptive requirements see section 4.6

4.4 Special warnings and precautions for use

Patients receiving immunosuppressive regimens involving combinations of medicinal product, including Mycophenolate Mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to 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 Mofetil 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).
Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in Mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.
Consideration should be given to reducing the total immunosuppression in patients who develop PML. In transplant patients, however, reduced immunosuppression may place the graft at risk.
Patients receiving Mycophenolate Mofetil should be monitored for neutropenia, which may be related to Mycophenolate Mofetil itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mycophenolate Mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu l$) it may be appropriate to interrupt or discontinue Mycophenolate Mofetil.
Patients should be advised that during treatment with Mycophenolate Mofetil vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.
Because Mycophenolate Mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation, Mycophenolate Mofetil should be administered with caution in patients with active serious digestive system disease.
Mycophenolate Mofetil is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. On theoretical grounds, therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Use of Mycophenolate Mofetil during pregnancy is associated with an increased risk of congenital malformations. Mycophenolate Mofetil therapy should not be initiated until a negative pregnancy test has been obtained (see section 4.6)
It is recommended that Mycophenolate Mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.
In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of Mycophenolate Mofetil with medicinal products that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate Mofetil.
The risk: benefit of Mycophenolate Mofetil in combination with tacrolimus or sirolimus has not been established (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.
Aciclovir: Higher aciclovir plasma concentrations were observed when Mycophenolate Mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucoronide 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 aluminum hydroxides: Absorption of Mycophenolate Mofetil was decreased when administered with antacids.
Cholestyramine: Following single dose administration of 1.5 g of Mycophenolate Mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40 % reduction in the AUC of MPA. (see section 4.4 and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of Mycophenolate Mofetil .
Medicinal products that interfere with enterohepatic circulation: Caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy of Mycophenolate Mofetil.
Ciclosporin A: Ciclosporin A (CsA) pharmacokinetics are unaffected by Mycophenolate Mofetil.
In contrast, if concomitant ciclosporin treatment is stopped, an increase in MPA AUC of around 30% should be expected.
Ganciclovir: Based on the results of a single dose administration study of recommended doses of oral Mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of Mycophenolate Mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and Mycophenolate Mofetil dose adjustment is not required. In patients with renal impairment in which Mycophenolate Mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.
Oral contraceptives: The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by coadministration of Mycophenolate Mofetil (see section 5.2).
Rifampicin: in patients not also taking ciclosporin, concomitant administration of Mycophenolate Mofetil 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 doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.
Sirolimus: In renal transplant patients, concomitant administration of Mycophenolate Mofetil and CsA resulted in reduced MPA exposures by 30-50% compared with patients receiving the combination of sirolimus and similar doses of Mycophenolate Mofetil (see section 4.4).
Sevelamer: decrease in MPA Cmax and AUC0-12 by 30% and 25%, respectively, were observed when Mycophenolate Mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer Mycophenolate Mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There is no data on Mycophenolate Mofetil with phosphate binders other than sevelamer.
Trimethoprim/sulfamethoxazole: No effect on the bioavailability of MPA was observed.
Norfloxacin and metronidazole: In healthy volunteers, no significant interaction was observed when Mycophenolate Mofetil was concomitantly administered with norfloxacin and metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30 % following a single dose of Mycophenolate Mofetil .
Tacrolimus: in hepatic transplant patients initiated on Mycophenolate Mofetil and tacrolimus, the AUC and Cmax of MPA, the active metabolite of Mycophenolate Mofetil, were not significantly affected by coadministration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of Mycophenolate mofetil (1.5 g BID) were administered to patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by Mycophenolate mofetil (see also section 4.4).
Other interactions: Co-administration of probenecid with Mycophenolate Mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substance 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 section 4.4).

4.6 Pregnancy and lactation

It is recommended that Mycophenolate Mofetil therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate Mofetil therapy, during therapy, and for six weeks following discontinuation of therapy (see section 4.5) Patients should be instructed to consult their physician immediately should pregnancy occur.
The use of Mycophenolate Mofetil is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. Mycophenolate Mofetil should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus. There is limited data from the use of Mycophenolate Mofetil in pregnant women. However, congenital

malformations including ear malformations i.e. abnormally formed or absent external/middle ear, have been reported in children of patients exposed to Mycophenolate mofetil in combination with other immunosuppressants during pregnancy. Cases of spontaneous abortions have been reported in patients exposed to Mycophenolate mofetil. Studies in animals have shown reproductive toxicity (see section 5.3).

Mycophenolate Mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to Mycophenolate Mofetil in breast-fed infants, Mycophenolate Mofetil is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

4.8 Undesirable effects

The following undesirable effects cover adverse reactions from clinical trials:

The principal adverse reactions associated with the administration of Mycophenolate Mofetil in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting and there is evidence of a higher frequency of certain types of infections (see section 4.4).

Malignancies:

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mycophenolate Mofetil , are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Lymphoproliferative disease or lymphoma developed in 0.6 % of patients receiving Mycophenolate Mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6 % of patients; other types of malignancy occurred in 1.1 % of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Opportunistic infections:

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4) The most common opportunistic infections in patients receiving Mycophenolate Mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5 %.

Children and adolescents (aged 2 to 18 years):

The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/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, 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 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 ≥ 1/10 and in ≥ 1/100 to <1/10 of patients treated with Mycophenolate Mofetil in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table.

Adverse reactions, probably or possibly related to Mycophenolate Mofetil, reported in patients treated with Mycophenolate Mofetil in renal, cardiac and hepatic clinical trials when used in combination with Ciclosporin and Corticosteroids.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class		**Adverse drug reactions**
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	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, 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 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, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in Mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. Agranulocytosis (≥1/1000 to <1/100) and neutropenia have been reported, therefore regular monitoring of patients taking Mycophenolate Mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with Mycophenolate Mofetil, some of which have been fatal.

Hypersensitivity:

Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction, have been reported.
Congenital disorders: see further details in section 4.6.

4.9 Overdose

Reports of overdoses with Mycophenolate Mofetil have been received from clinical trials and during post-marketing experience. In many of these cases, no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the medicinal product.
It is expected that an overdose of Mycophenolate Mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with Mycophenolate Mofetil should be interrupted or the dose reduced (see section 4.4).
Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic re-circulation of the drug (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents 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 Mofetil is correlated with MPA concentration. The mean bioavailability of oral Mycophenolate Mofetil, based on MPA AUC, is 94 % relative to IV Mycophenolate Mofetil. Food had no effect on the extent of absorption (MPA AUC) of Mycophenolate Mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax was decreased by 40 % in the presence of food. Mycophenolate Mofetil is not measurable systemically in plasma following oral administration. MPA at clinically relevant concentrations is 97 % bound to plasma albumin.
As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.
MPA is metabolized 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/1.73 m^2) were 28 – 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3 – 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of Mycophenolate Mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function:
In patients with delayed renal graft function post-transplant, mean MPA AUC(0–12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC(0-12h) was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of Mycophenolate Mofetil does not appear to be necessary.
Hepatic impairment:
In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.
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 Mofetil 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 behaviour of Mycophenolate Mofetil in the elderly has not been formally evaluated.
Oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by coadministration of Mycophenolate Mofetil (see section 4.5). A study of the coadministration of Mycophenolate Mofetil (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immuno suppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of Mycophenolate Mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

5.3 Preclinical safety data

In experimental models, Mycophenolate Mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or 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 20mg/kg/day The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients.
In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.
In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.
See 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

Mycophenolate Mofetil 500 mg Tablets:
cellulose microcrystalline
povidone (K-90)
hydroxypropylcellulose
talc
croscarmellose sodium
magnesium stearate
Tablet coating:
hypromellose 6 cps
titanium dioxide (E171)
macrogol 400
indigo carmine aluminum lake (E132)
red iron oxide (E172)
black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Mycophenolate Mofetil 500 mg film-coated Tablets: 1 carton contains 50 tablets (in blister packs of 10)
1 carton contains 150 tablets (in blister packs of 10). Not all pack sizes may be marketed.
Mycophenolate Mofetil 500 mg film-coated Tablets are packed in a white opaque PVC /PVdC-aluminum blisters packed in final carton along with package insert.

6.6 Special precautions for disposal

Because Mycophenolate Mofetil has demonstrated teratogenic effects in rats and rabbits, Mycophenolate Mofetil 500 mg film-coated tablets should not be crushed.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/12/2008

10 DATE OF REVISION OF THE TEXT

08/12/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3
PATIENT INFORMATION LEAFLET

accord

PACKAGE LEAFLET:
INFORMATION FOR THE USER

MYCOPHENOLATE MOFETIL 500mg FILM-COATED TABLETS

Mycophenolate Mofetil

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

In this leaflet:

1. What Mycophenolate Mofetil Tablets is and what it is used for

Immunosuppressants.

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

2. Before you take Mycophenolate Mofetil Tablets

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

Take special care with Mycophenolate Mofetil Tablets

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

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

Taking other medicines:

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

Any other medicines:
- Azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation).
- Cholestyramine (used to treat patients with high cholesterol).
- Rifampicin (antibiotic), antacids, phosphate binders (used in patient with chronic renal failure to reduce the absorption of phosphate) or any other medicines (including those you can buy without a prescription) that your doctor does not know about.

Vaccines:
- If you need to receive vaccines (live vaccines), your doctor will have to advise you what is indicated for you.

Taking Mycophenolate Mofetil Tablets with food and drink:

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

Pregnancy and breast-feeding:
- Do not take Mycophenolate Mofetil Tablets if you are breast-feeding.
- Ask your doctor for advice before taking any medicine. You must not use Mycophenolate Mofetil Tablets during pregnancy unless clearly indicated by your doctor.
- 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 Tablets, whilst taking Mycophenolate Mofetil Tablets, and for six weeks after you have stopped taking Mycophenolate Mofetil Tablets. This is because Mycophenolate Mofetil Tablets 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 Tablets has not been shown to impair your ability to drive or operate machinery.

3. How to take Mycophenolate Mofetil Tablets

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

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

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

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

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

Liver transplant:
Adults:
The first dose of oral Mycophenolate Mofetil Tablets will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medications. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning then 3 tablets in the evening.
Children:
No data are available to recommend the use of Mycophenolate Mofetil Tablets in children who have received a liver transplant.

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

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

If you take more Mycophenolate Mofetil Tablets than you should
If you take more Mycophenolate Mofetil Tablets than you have been told to take, or if someone else accidentally takes Mycophenolate Mofetil Tablets, immediately see a doctor or go to a hospital straight away.

If you forget to take Mycophenolate Mofetil Tablets
If you forget to take your medicine at any time, take it as soon as you remember, then continue to take it at the usual times. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Mycophenolate Mofetil Tablets
Stopping your treatment with Mycophenolate Mofetil Tablets 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 further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, Mycophenolate Mofetil Tablets can cause side effects, although not everybody gets them. Some of the more usual problems are diarrhoea, fewer white cells and/or red cells in your blood, infection and vomiting. 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.
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.

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, such as infections of the brain, 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, lethargy, difficulty in sleeping, pains (such as abdominal, chest, joint/muscle, pain on passing urine), headache, flu symptoms and swelling.

Other unwanted effects may include:

Disorders of the skin such as acne, cold sores, shingles, 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, flatulence and mouth ulcers.

Disorders of the nerves and senses such as convulsions, tremor, dizziness, depression, drowsiness, numbness, muscle spasms, anxiety, changes in thinking or mood.

Metabolic, blood and vascular disorders such as weight loss, gout, high blood sugar, bleeding, clots and bruises, change in blood pressure, abnormal heart beat and dilation of blood vessels may be seen.

Disorders of the lungs such as pneumonia, bronchitis, shortness of breath, cough, fluid on the lungs/chest cavity, sinus problems.

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

5. How to store Mycophenolate Mofetil Tablets

- Do not store above 25°C. Keep the blister in outer carton in order to protect from light.
- Keep out of the reach and sight of children.
- Do not use the Mycophenolate Mofetil Tablets after the expiry date, which is stated on the carton (EXP). The expiry date refers to the last day of that month.
- Always return any leftover medicine to your pharmacist. Only keep it if your doctor tells you to.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Mycophenolate Mofetil Tablets contain:
The active substance is 500mg as mycophenolate mofetil.
The other ingredients are:
Core tablet: cellulose microcrystalline (Avicel PH 102), povidone (k-90), hydroxypropyl cellulose, croscarmellose sodium, talc, magnesium stearate.
Coating materials: hypromellose 6 cps, titanium dioxide (E171), macrogol 400, iron oxide red (E172), indigo carmine aluminium lake (E132), iron oxide black (E172).

What Mycophenolate Mofetil Tablets looks like and content of the pack:
Mycophenolate Mofetil Tablets 500mg are purple, colored, capsule shaped, biconvex, film coated tablets debossed "AHI" on one side and "500" on other side.

Mycophenolate Mofetil Tablets are available in blisters in packs of 50 tablets and 150 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder: Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK.

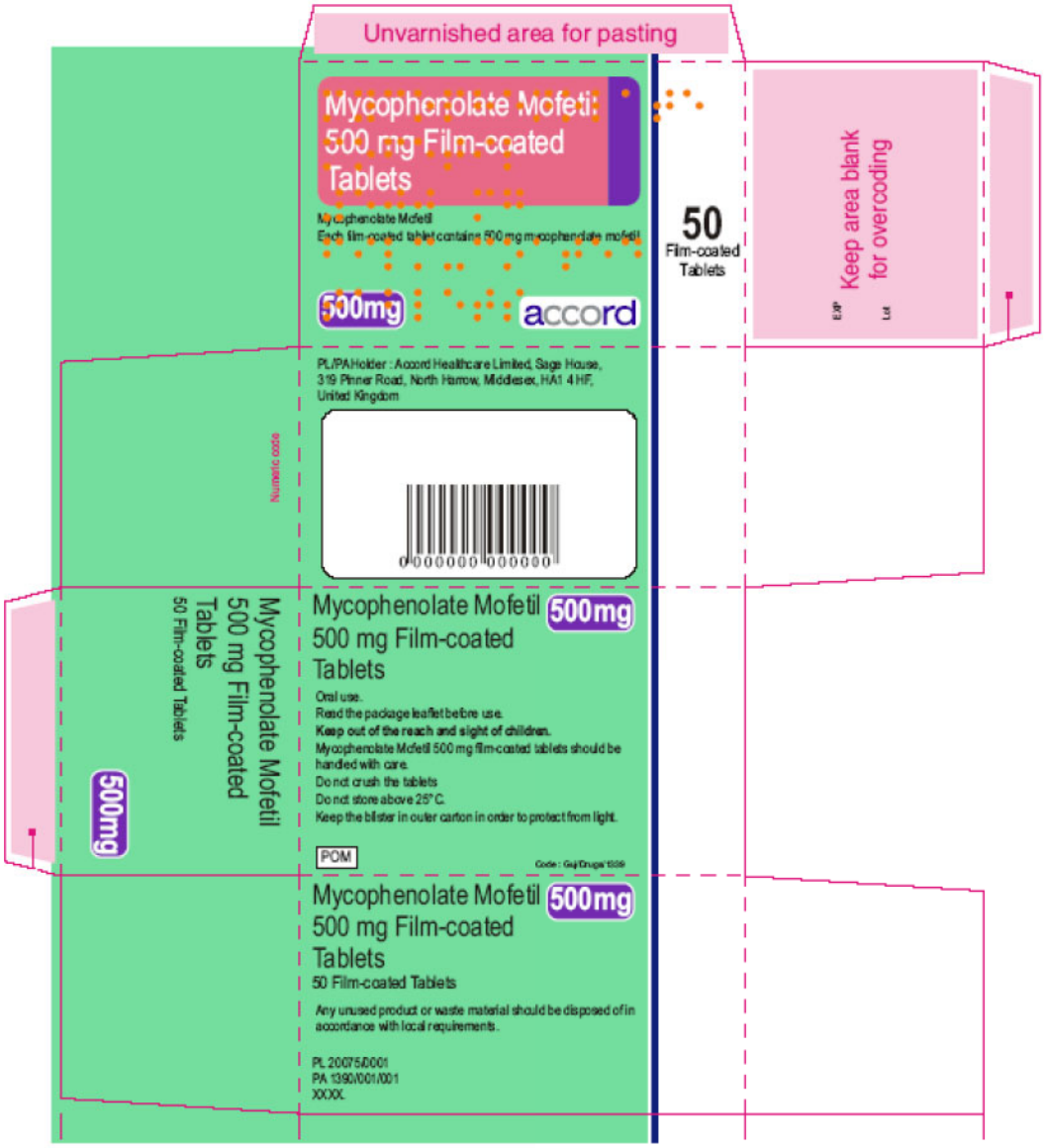
Manufacturer:
CEMELOG- BRS
2040 Budaors, Vasut u.2. Hungary

Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow,
Middlesex, HA1 4HF, UK

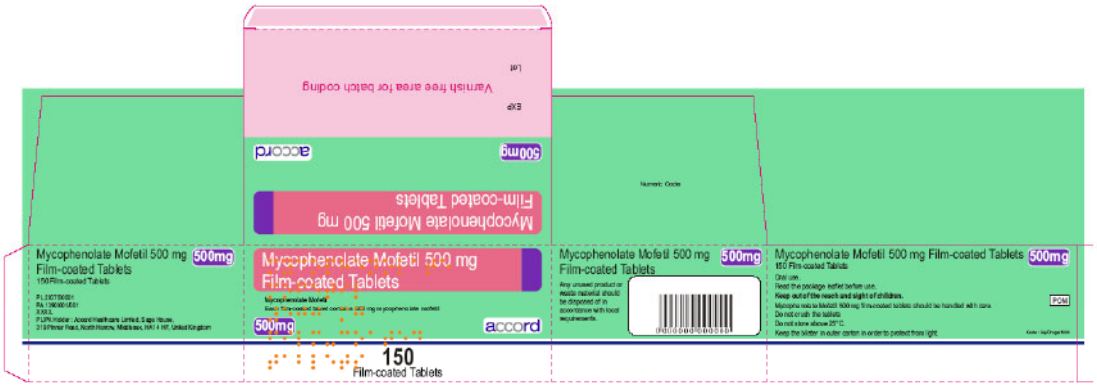
The leaflet was last approved in 10/2008

Module 4
Labelling

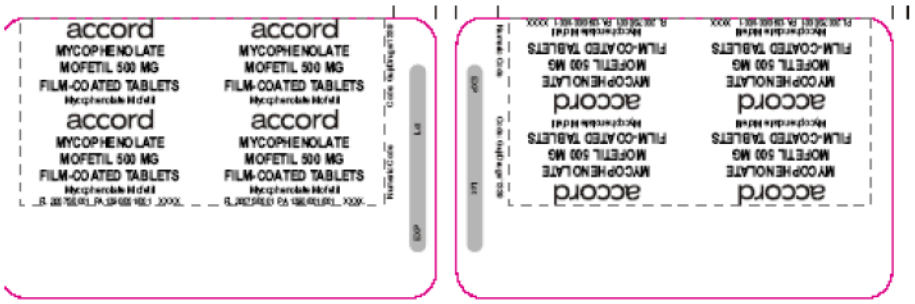
Carton-
Pack size- 50 film coated tablets



Carton-
Pack size- 150 film coated tablets


Mycophenolate Mofetil 500 mg Film-coated Tablets
500mg
accord
Mycophenolate Mofetil 500 mg Film-coated Tablets
150 Film-coated Tablets

Blister


accord
MYCOPHENOLATE MOFETIL 500 MG FILM-COATED TABLETS
Mycophenolate Mofetil
EXP
Lot

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mycophenolate Mofetil 500 mg tablets, in the prophylaxis of acute transplant rejection in patients receiving allogaenic renal, cardiac or hepatic transplants, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Mycophenolate Mofetil 500mg Film Coated Tablets, has been shown to be a generic medicinal product of CellCept 500mg Tablets which was first granted to Roche Registration Ltd, registered via the centralised procedure in the EU since 14th February 1996.

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 allogaenic renal, cardiac or hepatic transplants.

Mycophenolate Mofetil 500 mg tablets are indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

No new preclinical or clinical studies were conducted and none are required for an application of this type. This application for a generic product refers to CellCept 500mg Tablets, which has been licensed within the EEA for over 10 years. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release 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 RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

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. 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.

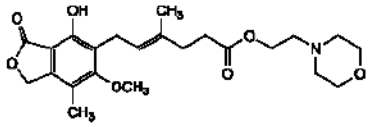
II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Mycophenolate Mofetil 500mg Film Coated Tablets
Name(s) of the active substance(s) (INN)	Mycophenolate Mofetil
Pharmacotherapeutic classification (ATC code)	Immunosuppressive agent (LO4AA06)
Pharmaceutical form and strength(s)	Film-Coated Tablet, 500mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1055/01/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Portugal, Sweden, Slovenia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland Slovak Republic and Romania
Marketing Authorisation Number(s)	PL 20075/0001
Name and address of the authorisation holder	Accord Healthcare Ltd Sage House, 319 Pinner Road, Middlesex, HA1 4HF

III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance

General Information
Nomenclature
INN: Mycophenolate Mofetil

Structure



Description:	White to off-white, crystalline powder
Solubility:	Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.
Chemical name:	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
or	
	mycophenolic acid 2-(4-morpholinyl)ethyl ester
Molecular formula:	$C_{23}H_{31}NO_7$
Molecular Weight	433.5

Manufacture
An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance mycophenolate mofetil. An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The active substance is packed in an inner transparent and an outer black low density polyethylene (LDPE) bags. The LDPE bags are strapped with cable ties and stored in high density polyethylene (HDPE) drums. Satisfactory specifications and certificates of analysis for the primary packaging components are provided.

Satisfactory batch data for three 51kg batches are provided by the active substance manufacturer and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a re-test period of 36 months. This is accepted.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients hydroxypropyl cellulose, croscarmellose sodium, povidone K90, microcrystalline cellulose, talc and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is magnesium stearate. A satisfactory TSE certificate of suitability has been provided for the supplier of magnesium stearate.

Dissolution and impurity profiles

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on three production scales, this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is packaged in blisters composed of aluminium, polyethylene chloride (PVC) and polyvinylidene chloride (PVdC). Specifications and a certificate of analysis for the packaging type used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 50 and 150 tablets. Not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory with the following specific storage conditions; "Do not store above 25 °C" and "Keep the blister in the outer carton in order to protect from light".

Conclusion

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

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

III.2 Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of mycophenolate mofetil are well known. As mycofenolate mofetil is a widely used, well-known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate. An adequate overview has been written by as suitably qualified person.

There are no objections to the approval of mycophenolate mofetil from a non-clinical point of view.

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 conducted a bioequivalence study (project 064-05) in order to confirm that the product Mycophenolate Mofetil 500 mg tablet is essentially similar to the reference product. As the batch used in the study was limited (30,000 tablets) the applicant has submitted an additional study (214-06) with batch size (115,000 tablets). Both studies are summarised below.

Bioequivalence study – Project 064-05

A Two-Way Crossover Bioavailability Study of Two formulations of Mycophenolate Mofetil 500 mg Tablets in Healthy Adult Human Male Subjects Under Fasting Conditions

Methods

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.

The study was conducted under GCP guidelines.

A single dose of 500 mg of the investigational products was administered orally to each subject in each period after an overnight fast. A washout period of 17 days was maintained between the two dosing days in each group.

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.

Assessor's comment
Blood sampling and washout period are adequate. As co-administration of food is known to have no effect in AUC but only in C_{max} in renal transplant patients the administration of study drugs under fasting conditions is also satisfactory.
The choice of a single dose 500 mg study is justified as 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:
Mycophenolate mofetil 500 mg tablets.

Reference:
CellCept 500 mg tablets By Roche Registration Ltd, UK

Healthy male subjects aged between 18 and 55 years were enrolled in the study.
Two subjects discontinued on their own accord after period I and one subject was withdrawn after period I on medical grounds.

The plasma samples were analysed using a validated LC-MS/MS method. T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λz, $t½$ and AUC%Extrap-obs were analysed.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for un-transformed 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 Mycophenolic acid are shown below:

Geometric Least Squares Mean, Ratios and 90% CI for Mycophenolic Acid

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	14869.076	15832.672	106.5	96.06-118.03
AUC_{0-t} (ng.h/ml)	27686.475	27381.734	98.9	95.65-102.26
$AUC_{0-\infty}$(ng.h/ml)	29027.115	28693.114	98.8	95.69-102.11

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

> ***Assessor's comment:***
> The results of the study showed that the test product and reference product are bioequivalent as the confidence intervals for C_{max} and AUC fall within the acceptance criteria ranges of 80-125% in line with current guidelines. However, as the batch size used in this study was limited to 30,000 tablets the applicant has conducted a second study in a larger batch size test.

Study 214-06:

The study was conducted according to GCP principles.

Design & Methods

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 500 mg dose of the investigational products 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. The subjects were not allowed to lie down for three hours after dosing, and were to remain fasting for 4 hours after dose. There was to be a washout period of 9 days between the two dosing days in each group. Serial blood sampling before dosing and up to 48 hours after drug administration was carried out in each group. After sample preparation, the samples were stored in -65ºC±10 ºC until analysis.

Test:
Mycophenolate mofetil 500 mg tablet (Batch size 115,000).

Reference:
Cellcept tablets 500 mg (Hoffman La Roche AG, Germany).

RMS Assessor's comment:
As the application concerns a conventional immediate-release formulation, a single-dose study is sufficient. There are no major deviations from dose linearity of MMF, and a 500 mg dose is adequate. There is no clinically relevant food effect on absorption of MMF, and therefore a study in the fasting state is appropriate. Blood sampling and washout periods are adequate. Batch size of the test product complies with current CHMP guidelines.

Study Population

Healthy male subjects aged between 18 and 55 years were enrolled in the study.

Analytical methods

Plasma samples were analysed for MMF and MPA concentrations using a validated LC-MS/MS method at the Bioanalytical facility of Lambda Therapeutic Research Ltd, Ahmedabad. The linear range of the method was 0.051 – 9.97 ng/ml for MMF and 52.7 – 24992 ng/ml for MPA. The assay showed acceptable within- and between-batch accuracy and precision for both analytes. For MMF, the recovery was 87.9%, 99.4% and 92.11% for low medium and high QC samples, respectively. For MPA, recovery was 76.0%, 83.4% and 82.2%, respectively. Carbamazepine was used as internal standard. The mean recovery for internal standard was 92.2%. No matrix effect was observed.

Sufficient dilution integrity was shown for 1/5 and 1/10 dilution for both analytes. Long-term stability was shown for MMF and MPA in human plasma containing EDTA for 280 days at -65ºC±10ºC. The analytes were shown to be stable for three freeze-thaw cycles. Benchtop stability (on dry ice) was shown fore 6 hours.

Re-analysis of samples was performed according to criteria specified in the internal SOP for re-assay. There were 15 re-analysed samples for MPA (of a total of 2028 samples), and the most common reason was 'concentration above the highest standard' (13/15 re-assays).

RMS Assessor's comment: The analytical method was adequately validated and showed acceptable performance.

Pharmacokinetic Variables

Pharmacokinetic parameters were calculated using non-compartmental methods. According to protocol, the bioequivalence evaluation was to be based on the variables C_{max}, AUC_{0-t} and AUC_{inf} for the active metabolite MPA since after absorption, the conversion of MMF to

MPA is rapid and complete and MMF concentrations are barely measurable in plasma after oral administration.

The protocol pre-specified that for any subject that had an extrapolated area of >20% of AUC_{inf}, the parameter AUC_{inf} would be excluded from the statistical analysis.

Statistical methods

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for un-transformed and ln-transformed PK parameters, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ were computed for MPA. Only descriptive statistics were reported for MMF. The protocol pre-specified that bioequivalence was to be concluded if the 90% confidence intervals (CIs) for the ln-transformed pharmacokinetic parameters for MPA were within 80-125% for AUC parameters and within 75-133% for C_{max}.

Results

The pharmacokinetic parameters for MMF and MPA in the second bioequivalence study are shown in Tables 1 and 2 below. The results of the statistical evaluation of bioequivalence are shown in Table 3.

Table 1. Descriptive Statistics of Formulation Means for Mycophenolate Mofetil, MMF. Study 214-06

Parameters	Mean ± SD (Un-transformed data)	
	Reference Product	Test Product
T_{max} (h)	0.66[a)]	0.66[a)]
C_{max} (ng/ml)	2.28 ± 2.02	2.71 ± 5.59
AUC_{0-t} (ng.h/ml)	2.08 ± 2.02	2.02 ± 1.99
$AUC_{0-\infty}$(ng.h/ml)	2.26 ± 2.26[b)]	2.22 ± 2.11[c)]
t½ (h)	1.22 ± 1.20[b)]	1.13 ± 1.06[c)]

[a)] Tmax is given as Median value
[b)] n=32
[c)] n=36

Table 2. Descriptive Statistics of Formulation Means for Mycophenolic Acid, MPA. Study 214-06 (n=39)

Parameters	Mean ± SD (Un-transformed data)	
	Reference Product	Test Product
T_{max}(h)	0.66[a)]	0.66[a)]
C_{max} (ng/ml)	13646 ± 5468	14425 ± 6241
AUC_{0-t} (ng.h/ml)	25511 ± 5182	27073 ± 4910
$AUC_{0-\infty}$(ng.h/ml)	27130 ± 5164	28749 ± 5225
t½ (h)	10.0 ± 3.7	10.6 ± 4.4

[a)] Tmax is given as Median value

Table 3. Geometric Least Squares Mean and results of statistical evaluation for Mycophenolic Acid, MPA. Study 214-06 (n=39)

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	12727	12130	104.9	85.5 - 128.8
AUC_{0-t} (ng.h/ml)	26614	24985	106.5	102.7 - 110.4
$AUC_{0-\infty}$ (ng.h/ml)	28255	26627	106.1	102.3 - 110.1

No subjects had predose concentrations of MMF or MPA, indicating that the washout period was sufficient. The mean extrapolated area for AUC_{inf} of MPA was 6.1% and 5.1% for the reference and test products, respectively, and no subjects had an extrapolated area exceeding 20%. For MMF, there were 7 and 3 subjects having an extrapolated area >20% for the reference and test formulation, respectively, and they were therefore, per protocol, not included in the summary statistics for AUC_{inf} and $t_{1/2}$ for MMF.

Conclusion

The results of the bioequivalence study 214-06 show that the test and reference products are bioequivalent and support the results of the first study (study 064-05) submitted in the original dossier. However, as Cmax CI were not within the conventional acceptance range of 80-125% it was considered by some CMS that bioequivalence was not shown with this second study.

The procedures were referred to the Coordination Group for Mutual recognition and Decentralised Procedures (CMD(h)) due to potential serious risk to public health concerns raised on the suitability of the bioequivalence studies provided in support of the applications. At the CMD(h) meeting, it was acknowledged that in the first study there was a deviation from the normal expected batch size to be used for the biobatch. However, the RMS considered that the applicant had provided adequate data to show that the biobatch was representative of production scale. In this study bioequivalence was demonstrated in line with normal acceptance criteria. Member States agreed that this should be considered the pivotal biostudy. To finalise the procedures and not to deviate from the generally accepted standards described in the NfG on bioequivalence, the applicant will limit production scale to the batch size used in biostudy 064-05. Further supportive data would be provided before any increase in commercial batch size is approved.

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.

BENEFIT RISK ASSESSMENT

The benefit-risk ratio is considered favourable.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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 Mofetil 500mg Film Coated Tablets and CellCept 500 mg tablets (Roche Registration Ltd, UK).

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 products and the innovator products are interchangeable. Extensive clinical experience with mycophenolate mofetil considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
23/2/2009	Type II	To submit the data for the new Bioequivalence study, on a 110,000 tablets batch size as per our commitment made during referral for the captioned procedure. To also include an additional batch size of 110.000 to the product licence.	Approved on 29th July 2009

Annex 1

Reference: **PL 20075/0001-0005; UK/H/1055/II/004**
Product: **Mycophenolate Mofetil 500mg film-coated tablets**
Marketing Authorisation Holder: **Accord Healthcare Limited**
Active Ingredient(s): **Mycophenolate Mofetil**

Reason:
To submit the data for the new bioequivalence study, on a 110,000 tablets batch size as per the commitment made during referral for the captioned procedure. To also include an additional batch size of 110,000 to the product licence.

Introduction
The applicant(s) made the following commitment during the referral to CMDh (EMEA/CMDh/454960/2008) for the procedure UK/H/1055/01/DC.
The applicant limits the commercial production scale to 30,000 tablets at present.

- Perform and submit a new bioequivalence study to support the scale up in manufacture intended commercial scale batches (>100,000 tablets) as part of any future variation application to increase the batch size above 30,000 tablets and proving bioequivalence between this batch and Reference.

This variation addresses that commitment.

Proposed changes
To increase the commercial manufacturing batch size to 110,000 tablets, supported by an appropriate bioequivalence study.

Supporting Evidence
Variation application form
Updated module 2.5 (Clinical overview)
Updated section 3.2.P.3.2 (Batch formula)
Updated section 3.2.P.3.3 (Description of manufacturing process and process controls)
Updated module 3.2.R.1
New biostudy performed between test product and reference CellCept.
Certificate of analysis for reference and test product

Evaluation

QOS / Clinical overview
The clinical overview is satisfactory.

Module 3
The revised batch formula has been provided.

The revision to 3.2.P.3.3 includes the scope for equivalent process equipment used in the up-scaled process.

The process validation protocol is satisfactory for the proposed batch size of 110,000 tablets.

Bioequivalence study- Project 361-08

A Two-Way Crossover Bioavailability Study of two Formulations of Mycophenolate Mofetil 500mg Tablets in Healthy Adult Human Male Subjects under Fasting Conditions

Methods
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. Although this was an open study the analysts performing the assay on collected plasma samples were unaware of the sequence of administration to individual subjects. This is acceptable.

The study was conducted under GCP guidelines

A single dose of 500mg of the test product with a single dose of the reference product were administered orally to each subject in each period after an overnight fast. A washout period of 14 days was maintained between the two dosing days in each group which is sufficient to prevent carry-over into the second study period.

Serial blood sampling before dosing and up to 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.

Test:
Mycophenolate mofetil 500mg tablets

Reference:
CellCept 500mg tablets by Roche Registration Ltd, UK

The protocol specifies bioequivalence acceptance ranges of 80-125% for AUC_{0-t} , AUC_{∞} and C_{max}. These are in line with the agreed acceptance ranges for this drug substance.

Statistical plan
An adequate statistical plan is provided and the planned statistical methods are conventional. Log-transformed data for AUC_t, AUC_{inf} and C_{max} analysed by ANOVA. T_{max} was analysed non-parametrically.

According to the relevant guidance (see Questions & Answers on the Bioavailability and Bioequivalence Guideline CHMP/EWP/40326/06), bioequivalence should preferably be based on data for the parent drug, i.e. mycophenolate mofetil. However, in this case, there are arguments to allow demonstration of bioequivalence to be based on data for the active metabolite mycophenolic acid. First mycophenolate mofetil is an inactive prodrug. Second, plasma levels of mycophenolate mofetil are very much lower than that of the active metabolite mycophenolic acid. Therefore, the applicant's statistical analysis is considered adequate, and data obtained for the active metabolite can be considered as primary basis for assessing bioequivalence.

Handling of dropouts and missing data and other protocol deviations
Four subjects were withdrawn from the study on medical grounds, four withdrew from the study of their own accord and one subject was withdrawn due to protocol deviation. Proposals for handling drop-outs and other missing data are given and are acceptable.

The plasma samples were analysed using a validated LC-MS/MS method. T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λz, t½ and AUC%Extrap-obs were analysed.

Statistical analyses
The results for main pharmacokinetic parameters are reported as follows:

Summary results for the bioequivalence study For Mycophenolic acid

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

Table 1. Geometric Least Squares Mean and results of statistical evaluation for Mycophenolic Acid, MPA. Study 361-08

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	15484	16212	104.7	94.13-116.46%
AUC_{0-t} (ng.h/ml)	27954	28034	100.3	98.26-102.36%
$AUC_{0-\infty}$(ng.h/ml)	29867	29922	100.2	98.05%-102.36%

A summary of protocol deviations is provided and are considered unlikely to impact the study results. This is accepted.

The 90% confidence intervals for test/reference lie within the acceptance criteria pre-specified in the study protocol. Bioequivalence of the test product to the reference formulation appears to have been satisfactorily demonstrated in accordance with CHMP criteria.

GCP certification
Satisfactory documentary evidence is provided to show that the biostudy was carried out according to current standards of Good Clinical Practice and that original and complete study records are available for inspection.

Conclusion
The proposed revision to the manufacturing process to incorporate a larger batch scale is acceptable. The analysis of the pharmacokinetic data for mycophenolic acid (MPA) is satisfactory. Bioequivalence has been demonstrated between the applicant's Mycophenolate mofetil 500mg Film Coated Tablets and the reference product CellCept Roche Registration LTD, UK

Decision Granted 29/07/2009