COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mycofenolaat Mofetil Accord 250 mg capsules

(mycophenolate mofetil)

NL/H/4567/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Mycofenolaat Mofetil Accord 250 mg capsules. The procedure was finalised in the United Kingdom (UK/H/1331/001/DC). After a transfer in 2018, 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

Mycophenolate Mofetil 250mg Capsules

Mycophenolate mofetil

UK/H/1331/01

PL 20075/0097

Accord Healthcare Ltd

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Module 1

Product Name	Mycophenolate Mofetil 250 mg Capsules
Type of Application	Complex Abridged Decentralised (Article 10.1)
Active Substance (INN)	Mycophenolate mofetil
Pharmacotherapeutic Classification (ATC)	L04AA06
Pharmaceuctical Form and Strength	Capsules, hard, 250 mg
Procedure Numbers	UK/H/1331/01/DC
RMS	UK
CMS	BG, CY, CZ, DE, EE, EL, ES, FI, FR, HU, LT, LV, MT, PL, PT, RO, SI and SK
Start Date	12/02/2008
End Date	27.04.2009 (Day 210)
MA Number	PL 20075/0097
Name and address of MA holder	Accord Healthcare Limited Sage House 319 Pinner Road North Harrow Middlesex HA1 4HF

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mycophenolate Mofetil 250 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg mycophenolate mofetil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Light blue/peach size '1' hard gelatin capsule imprinting with 'MMF' on cap and '250' on body, containing white to off white powder

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 capsules 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 capsules 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 capsules at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Children (< 2 years):
There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dose 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 and adolescents:
No data are available for paediatric cardiac transplant patients, therefore use in this patients group is not recommended until further data to support this is available.

Use in hepatic transplant:

Adults:
Intravenous 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 and adolescents: No data are available for paediatric hepatic transplant patients~~.~~ , therefore use in this patients group is not recommended until further data to support this is available.

Use in elderly (≥65 years):
The recommended dose of 1g 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}•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; dose reduction or interruption of mycophenolate mofetil is not required. There is no basis for mycophenolate mofetil dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

4.3 Contraindications

Hypersensitivity reactions to mycophenolate mofetil have been observed (see section 4.8). Therefore, mycophenolate mofetil is contraindicated in patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid.

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 mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and ultra violet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Patients receiving mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients treated with immunosuppressants, including mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

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

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 (area under the curve) 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 glucuronide of MPA) pharmacokinetics (MPAG increased by 8 %) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids with magnesium and aluminium hydroxides: absorption of mycophenolate mofetil was decreased when administered with antacids.

Cholestyramine: following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g three times a day (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 were 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 intravenous 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 co-administration 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 co-administration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g taken twice a day [BID], morning and evening) were administered to patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see section 4.4).

Other interactions: co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

Live vaccines: live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see 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 breast-feeding 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, cytomegalovirus (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 ≥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, reported in patients treated with Mycophenolate 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**
Investigations	Very common	----
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased
Cardiac disorders	Very common	----

	Common	Tachycardia
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leucocytosis
Nervous system disorders	Very common	----
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
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
Renal and urinary disorders	Very common	----
	Common	Renal impairment
Skin and subcutaneous tissue disorders	Very common	----
	Common	Skin hypertrophy, rash, acne, alopecia,
Musculoskeletal and connective Tissue disorders	Very common	----
	Common	Arthralgia
Metabolism and nutrition disorders	Very common	-----
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
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
Vascular disorders	Very common	-----
	Common	Hypotension, hypertension, vasodilatation
General disorders and administration site conditions	Very common	----
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia,
Hepatobiliary disorders	Very common	----
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Psychiatric disorders	Very common	-----
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia

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, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil. Agranulocytosis (≥1/1000 to

<1/100) and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate mofetil, some of which have been fatal.

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: L04A A06

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.

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 intravenous 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 cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.

A negligible amount of substance is excreted as MPA (< 1 % of dose) in the urine. Orally administered radiolabelled mycophenolate mofetil results in complete recovery of the administered dose with 93 % of the administered dose recovered in the urine and 6 % recovered in the faeces. Most (about 87 %) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100µg/ml), small amounts of MPAG are removed.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and C_{max} approximately 40 % lower compared to the late post-transplant period (3 – 6 months post-transplant).

Renal impairment:
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml•min^{-1}•1.73 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 post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

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

Oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by co-administration of mycophenolate mofetil (see section 4.5). A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (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 $mg•kg^{-1}•day^{-1}$. 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 $mg•kg^{-1}•day^{-1}$ 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 $mg•kg^{-1}•day^{-1}$ (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 $mg•kg^{1}•day^{-1}$ (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

Refer to section 4.6.

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended 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 contents:
Cellulose microcrystalline
Hydroxy propyl cellulose
Povidone K 90
Croscarmellose sodium

Talc
Magnesium stearate

Capsule shell:
Gelatin
Sodium lauryl sulfate
FD & C Blue 2 (E132)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Black Ink composition:
Shellac
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

21 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Mycophenolate Mofetil 250 mg capsules are packed in PVC/PVDC/Aluminium blister.
1 carton contains 100 capsules (in blister packs of 10).
1 carton contains 300 capsules (in blister packs of 10).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0097

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/06/2009

10 DATE OF REVISION OF THE TEXT

18/06/2009

Module 3

Product Information Leaflet

accord

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Mycophenolate Mofetil 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 further questions, please 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 CAPSULES IS AND WHAT IT IS USED FOR

Immunosuppressant.

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

2. BEFORE YOU TAKE MYCOPHENOLATE MOFETIL CAPSULES

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

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

Mycophenolate Mofetil 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.
Talk to your doctor before you start to take Mycophenolate Mofetil Capsules if:
- you are taking any medicines containing: azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation), cholestyramine (used to treat patients with high blood cholesterol), antacids, rifampicin (antibiotic), phosphate binders (used in patients with chronic renal failure to reduce the absorption of phosphate)
- live vaccines should be avoided. Your doctor will have to advise you what is indicated for you.

Taking Mycophenolate Mofetil Capsules with food and drink
Taking food and drink has no influence on your treatment with mycophenolate mofetil.

Pregnancy and breast-feeding:
Do not take Mycophenolate Mofetil if you are breastfeeding.
You must not use Mycophenolate Mofetil during pregnancy unless clearly indicated by your doctor. Your doctor should advise you about using contraception before taking Mycophenolate Mofetil, whilst taking Mycophenolate Mofetil, and for 6 weeks after you have stopped taking Mycophenolate Mofetil. This is because Mycophenolate Mofetil may cause spontaneous abortions or damage, including problems with development of the ears, to your unborn baby. Tell your doctor straight away if you are pregnant, breast-feeding, become pregnant or plan to start a family in the near future.
Ask your doctor or pharmacist 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 MOFETIL CAPSULES

Always take Mycophenolate Mofetil Capsules 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 Capsules 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 Capsules 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 or split open.
- 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 Mofetil Capsules than you should
If you take more mycophenolate mofetil 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 Mofetil Capsules
If you forget to take your medicine at any time, take it as soon as you remember; then continue to take it at the usual times. Do not take a double dose to make up for a forgotten dose.

If you stop taking Mycophenolate Mofetil 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, mycophenolate mofetil can have side effects, although not everybody gets them.

Some of the more usual problems are 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 defense 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 Capsules, 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 CAPSULES

- Keep out of the reach and sight of children.
- Do not use Mycophenolate Mofetil Capsules after expiry date, which is stated on the label or carton after EXP. The expiry date refers to the last day of that month.
- Store below 30ºC.
- Do not use mycophenolate mofetil capsules if you notice any visible signs of deterioration.
- 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 Capsules contains:
The active substance is Mycophenolate Mofetil. Each capsule contains 250 mg of Mycophenolate Mofetil.

The other ingredients are: cellulose microcrystalline, hydroxy propyl cellulose, povidone K 90, croscarmellose sodium, talc & magnesium stearate.

Capsule Shell composition: Gelatin, sodium lauryl sulfate, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172),
FD & C Blue 2 (E132)

What Mycophenolate Mofetil Capsules looks like and content of the pack:
Mycophenolate Mofetil 250 mg capsules are light blue/peach size '1' hard gelatin capsules with imprinting with 'MMF' on cap and '250' on body, containing white to off white powder.

Mycophenolate Mofetil 250 mg Capsules are available in blister in packs of 100and 300' capsules.

Not all pack sizes may be marketed.

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

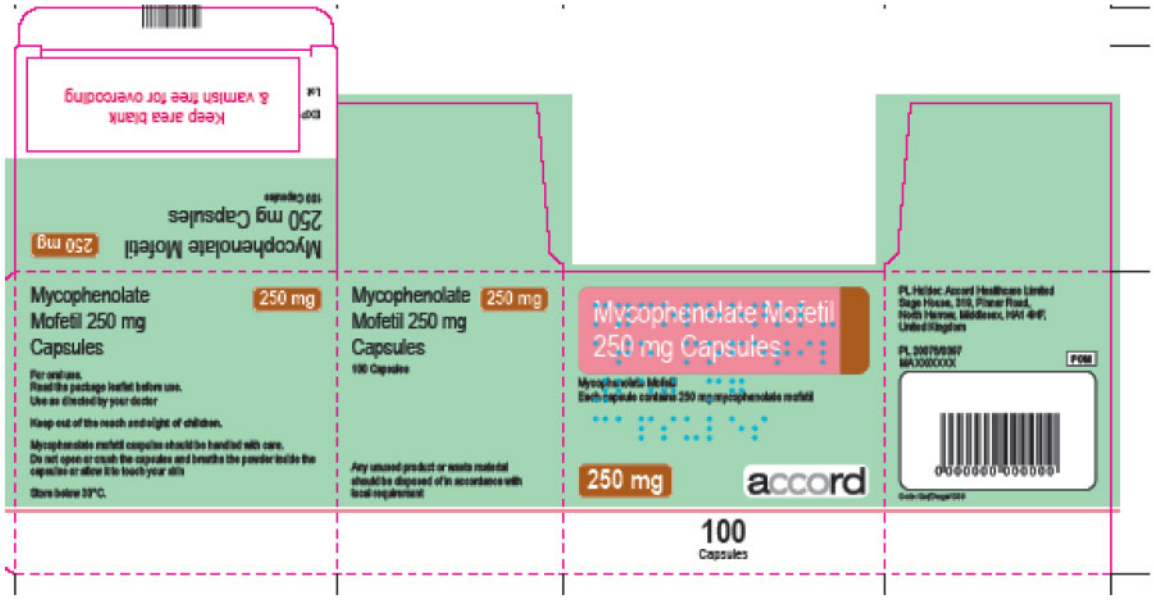
Manufacturer:
Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

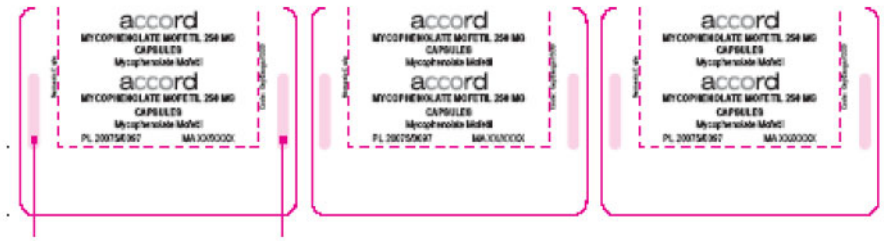
CEMELOG- BRS Limited
2040 Budaors, Vasut u.13.
Hungary

The leaflet was last approved in 05/2009.

Module 4

Labelling





Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mycophenolate Mofetil 250 mg Capsules, for the prevention of organ rejection following transplantation (see indication below), is approvable.

EXECUTIVE SUMMARY

About the product

Mycophenolate mofetil (MMF) is an anti-lymphocytic agent that is rapidly absorbed and de-esterified following oral or IV administration to form mycophenolic acid (MPA). The active metabolite MPA is a selective, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase. This inhibition leads to a nucleotide deficiency within cells that slows proliferative rate. In lymphocytes, a slow proliferation rate and changes to the surface glycosylation of adherence molecules render the lymphocytes less effective in recognising and eliminating allografts and organ transplants.

The proposed indication is:

For use in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites 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 as certification that acceptable standards of GMP are in place at those non-Community sites.

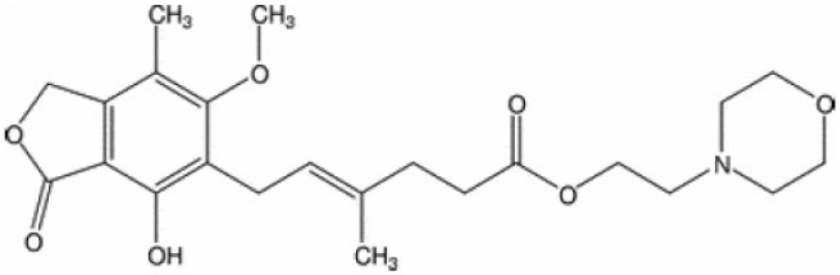
The CRO has confirmed that the study was conducted according to principles of GCP. The CRO was last satisfactorily inspected by the World Health Organisation in 2004. There is nothing in the dossier that suggests deviation from the principles of GCP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

Structure:



Description: White to off-white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

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. 2-morpholinoethyl(E) –6-4-hydroxy-6-methoxy –7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate
iii. 2-morpholinyl (E) –6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoiso benzo furan-5-yl)-4-methyl-4-hexenoate.

INN: mycophenolate mofetil

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

MW: 433.5 g mol^{-1}

III.1.3 General properties

Mycophenolate mofetil is a white to almost white crystalline powder, which is practically insoluble in water, freely soluble in acetone, soluble in methanol and sparingly soluble in anhydrous ethanol. Mycophenolate mofetil is optically inactive and has a melting point of about 96 °C.

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.

Mycophenolate mofetil is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided 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 retest period of 36 months, when stored in the original airtight container.

Drug Product

The proposed product composition has been provided and the other ingredients are:

Capsule contents:
Cellulose microcrystalline
Hydroxy propyl cellulose
Povidone K 90
Croscarmellose sodium
Talc
Magnesium stearate

Capsule shell:
Gelatin
Sodium lauryl sulfate
FD & C Blue 2 (E132)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Black Ink composition:
Shellac
Black iron oxide

The development of the product has been described, the choice of excipients is justified and their functions explained.. The product specifications cover appropriate parameters for this dosage form. Validations reports for the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. A shelf-life of 21 months has been proposed, which is considered acceptable.

Non-clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of mycophenolate mofetil are well known. As mycophenolate mofetil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. A satisfactory non-clinical overview by a suitably qualified person was provided.

Clinical aspects

Pharmacokinetics

The applicant has submitted a report of a clinical study to assess the bioequivalence of the proposed product Mycophenolate mofetil 250 mg capsules with the reference product Cellcept 250mg Capsules.

This was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover, comparative oral bioavailability study of Mycophenolate Mofetil 250 mg Capsules in healthy, adult, human male subjects under fasting conditions.

A single dose of test or reference product was administered to each subject in each period according to a randomisation schedule. The product was administered with 240 ml of water after a fast of at least 10 hours. There was a washout period of 11 days between each treatment period. Blood samples were collected over a period of 60 hours.

A total of twenty-six subjects in Group-A and twenty-eight subjects including Subject Nos. X-I and X-2 in Group-B were checked-in for the trial. Subject Nos. X-I and X-2 were checked-in for the trial, in order to account for any dropouts prior to dosing in Period-I.

As per the protocol, fifty-two subjects were dosed in Period-I of the trial. A total of fifty subjects (01-27, 29-38 and 40-52) completed the trial successfully. The plasma samples of these fifty subjects (01-27, 29-38 and 40-52), as well as the plasma samples of Subject Nos. 28 and 39 (withdrawn on medical grounds) were analyzed, as per the requirement of the protocol.

Mycophenolate mofetil and mycophenolic acid were quantified by a validated LC-MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by noncompartmental model using WinNonlin Professional Software Version 5.0.1 (Pharsight Corporation, USA).

The 90% parametric confidence intervals were calculated for the untransformed and ln-transformed pharmacokinetic parameters, Cmax AU0-t, and AUC0-∞ of the mycophenolate mofetil and mycophenolic acid. Bioequivalence of Test Product-B vs. Reference Product-A was to be concluded, if the 90% confidence interval fell within the acceptance range as defined below for In-transformed pharmacokinetic parameters, Cmax AU0-t, and AUC0-∞ of mycophenolate mofetil and mycophenolic acid.

Mycophenolate mofetil (n=50)

Parameters (Units)	In-transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	(B / A)%	
C_{max} (ng / mL)	1.953	1.797	108.7%	94.37-125.18%
AUC_{0-t} (ng . h / mL)	1.229	1.136	108.2%	97.12-120.55%
$AUC_{0-\infty}$ (ng . h / mL)	1.401	1.270	110.3%	98.29-123.85%

For Mycophenolic acid (n=50)

Parameters (Units)	In-transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	(B / A)%	
C_{max} (ng / mL)	10338.537	10165.717	101.7%	93.46-110.67%
AUC_{0-t} (ng . h / mL)	12185.159	11999.868	101.5%	98.02-105.19%
$AUC_{0-\infty}$ (ng . h / mL)	12884.070	12731.732	101.2%	97.64-104.88%

As could be expected the results for the levels of parent compound were low and variable. The 90% confidence intervals for AUC parameters as well as C_{max} were within the 80-125% limits for the metabolite. The upper value of Cmax was 125.18% for the parent compound which is just outside the upper limit of 125%. This was not judged to be clinically significant. It is judged that the test and reference tablets are bioequivalent.

Pharmacodynamics

No new data have been submitted and none are required.

Clinical efficacy

No novel efficacy data are supplied or required for this generic application. However, the applicant has provided a clinical overview that reviews the clinical trials published in the literature confirming the efficacy of mycophenolate. The review adequately summarises the data relating to the efficacy of mycophenolate.

Clinical safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of mycophenolate. No new safety issues have been identified.

Pharmacovigilance system

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

Risk Management Plan
None is proposed for this generic product. This is acceptable.

Product Literature
Satisfactory Summary of Product Characteristics, Patient Information Leaflet and labelling has been provided.

BENEFIT RISK ASSESSMENT

The use of mycophenolate is well established. It has recognised efficacy and acceptable safety.

The bioequivalence study demostrated that the applicant's mycophenolate mofetil 250 mg capsules are bioequivalent to the reference product CellCept® 250 mg capsules. The benefit risk assessment is considered positive and the marketing authorisation was approved.

Module 6

Steps taken after procedure

No non-confidential changed have been made to the marketing authorisation.