PACKAGE INSERT

MYCOFIT 250
(Mycophenolate Mofetil Capsules 250 mg)

Product Name

MYCOFIT 250

Strength of active substance

Each hard gelatin capsule contains:
Mycophenolate Mofetil Ph. Eur. 250 mg

Description

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

Active Ingredients:

Mycophenolate Mofetil

Inactive Ingredients:

Capsule filling:
Microcrystalline cellulose
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

Pharmacological properties

Pharmacodynamic properties

Mechanism of action

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.

Pharmacokinetic properties

Absorption

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 Cmax was decreased by 40 % in the presence of food.

Distribution

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 at clinically relevant concentrations is 97 % bound to plasma albumin.

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF´s side effects (diarrhoea, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1 % of dose) in the urine. Oral administration of radio labeled 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. By interfering with enterohepatic circulation of the drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC.

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

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).

Special populations

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 folds 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. In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients.

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.

Elderly:

Pharmacokinetic behaviour of Mycophenolate Mofetil in the elderly (≥65 years) has not been formally evaluated.

Patients taking oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by co-administration of Mycophenolate Mofetil. 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.

Indication

Mycofit is indicated for:

- Prophylaxis of acute organ rejection and treatment of refractory organ rejection in patients receiving allogeneic renal transplants.
- Prophylaxis of acute organ rejection and increased graft and patient survival in patients receiving allogeneic cardiac transplants.
- Prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Mycofit should be used concomitantly with cyclosporin and corticosteroids.

Recommended Dosage

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).

Standard dosage for treatment of refractory renal rejection: A dose of 1.5 g administered twice a day (daily dose of 3g) is recommended for management of refractory rejection.

Use in cardiac transplant

Adults
The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Use in hepatic transplant

Adults
The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

The initial dose of Mycofit capsules should be given as soon as possible following renal, cardiac or hepatic transplantation.

Use in special populations

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 $ml \bullet min^{-1} \bullet 1.73\ m^{-2}$), 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 postoperatively. 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:
Mycophenolic acid (MPA) 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.

Method of administration

Mycophenolate Mofetil Capsules should be taken orally.

Precautions to be taken before handling or administering the medicinal product

Because Mycophenolate Mofetil has demonstrated teratogenic effects in rats and rabbits, Mycophenolate Mofetil capsules should not be opened or crushed to 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.

Contraindications

Allergic reactions to Mycofit have been observed. Therefore, Mycofit is contraindicated in patients with hypersensitivity to Mycophenolate Mofetil or Mycophenolic acid.
Mycofit is contraindicated during pregnancy due to its mutagenic and teratogenic potential.
Mycofit is contraindicated in women of childbearing potential not using highly effective contraceptive methods.
Mycofit is contraindicated in women who are breastfeeding.

Special warnings and precautions for use

Neoplasms

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. 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 ultra violet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including Mycophenolate Mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. 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.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Mycophenolate Mofetil in combination with other immunosuppressants. In some of these cases switching Mycophenolate Mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on Mycophenolate Mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received Mycophenolate Mofetil in combination with other immunosuppressants. In some of these cases switching Mycophenolate Mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or

to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

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.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Mycophenolate Mofetil in combination with other immunosuppressants. The mechanism for Mycophenolate Mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of Mycophenolate Mofetil therapy. Changes to Mycophenolate Mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection.
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 should be advised that during treatment with Mycophenolate Mofetil, vaccinations may be less effective and the use of live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastro-intestinal

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. 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.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs of other classes which interfere with MPA's enterohepatic cycle e.g. cholestyramine, should be used with caution due to their potential to reduce plasma levels and efficacy of Mycophenolate Mofetil. It is recommended that Mycophenolate Mofetil

should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

Special populations

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals.

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45 - 49%) and congenital malformations (estimated rate of 23 - 27%) have been reported following MMF exposure during pregnancy. Therefore Mycophenolate Mofetil is contraindicated in pregnancy. Female and male patients of reproductive potential should be made aware of the risks and follow the recommendations (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Mycophenolate Mofetil. Physicians should ensure that women and men taking Mycophenolate Mofetil understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception

Because of the genotoxic and teratogenic potential of Mycophenolate Mofetil, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycophenolate Mofetil therapy, during therapy, and for six weeks after stopping the therapy; Unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with Mycophenolate Mofetil are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Mycophenolate Mofetil.

Interaction with other medicinal products and other forms of interaction

Aciclovir

Higher aciclovir plasma concentrations were observed when Mycophenolate Mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. 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 and proton pump inhibitors (PPIs)

Decreased MPA exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with Mycophenolate Mofetil. When comparing rates of transplant rejection or rates of graft loss between Mycophenolate Mofetil patients taking PPIs vs. Mycophenolate Mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when Mycophenolate Mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when Mycophenolate Mofetil was co-administered with PPIs.

Cholestyramine

Following single dose administration of 1.5 g of Mycophenolate Mofetil to normal healthy subjects pretreated with 4 g three times a day (TID) of cholestyramine for 4 days, there was a 40 % reduction in the AUC of MPA. 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. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30 - 50 % in renal transplant patients treated with Mycophenolate Mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of Mycophenolate Mofetil. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA´s enterohepatic cycle.

Telmisartan

Concomitant administration of Telmisartan and Mycophenolate Mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between Mycophenolate Mofetil patients with and without concomitant Telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

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 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 whom 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.

Rifampicin

In patients not also taking ciclosporin, concomitant administration of Mycophenolate Mofetil and rifampicin resulted in a 70% decrease in MPA exposure (AUC 0-12 h). It is recommended to monitor MPA exposure levels and to adjust Mycophenolate Mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

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 sevelamer two hours after Mycophenolate Mofetil intake to minimize the impact on the absorption of MPA. There are 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 or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30 % following a single dose of Mycophenolate Mofetil.

Ciprofloxacin and amoxicillin plus clavulanic acid

Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and

to cease within a few days of antibiotic discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Mycophenolate Mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tacrolimus

In hepatic transplant patients initiated on Mycophenolate Mofetil and tacrolimus, the AUC and 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 BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by Mycophenolate Mofetil.

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.

Paediatric population

Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation

Contraception in males and females

Mycophenolate Mofetil is contraindicated in women of childbearing potential who are not using highly effective contraception.
Because of the genotoxic and teratogenic potential of Mycophenolate Mofetil, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycophenolate Mofetil therapy, during therapy, and for six weeks after stopping the therapy; Unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with

Mycophenolate Mofetil are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Mycophenolate Mofetil.

Pregnancy:

Mycophenolate Mofetil is contraindicated during pregnancy. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.
Female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counseled regarding pregnancy prevention and planning.

Before starting Mycophenolate Mofetil treatment, women of child bearing potential should have a pregnancy test in order to exclude unintended exposure of the embryo to Mycophenolate. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml are recommended; the second test should be performed 8 – 10 days after the first one and immediately before starting Mycophenolate Mofetil. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.
Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to Mycophenolate Mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than Mycophenolate Mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to Mycophenolate Mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than Mycophenolate Mofetil).

Congenital malformations, including reports of multiple malformations, have been observed post marketing in children of patients exposed to Mycophenolate Mofetil in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear), external auditory canal atresia• Congenital heart disease such as atrial and ventricular septal defects
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits
- Abnormalities of the eye (e.g. coloboma)
- Malformations of the fingers (e.g. polydactyly, syndactyly)
- Tracheo-Oesophageal malformations (e.g. oesophageal atresia)
- Nervous system malformations such as spina bifida
- Cardiac abnormalities such as atrial and ventricular septal defects.

In addition there have been isolated reports of the following malformations:

- Microphthalmia
- congenital choroid plexus cyst
- septum pellucidum agenesis
- olfactory nerve agenesis.

Breastfeeding

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 breastfed infants, Mycophenolate Mofetil is contraindicated in breastfeeding mothers.

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.

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.

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. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% 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 1.6% to 4.2% of patients; other types of malignancy occurred in 0.7% to 2.1 % 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. 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 %.

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 events reported in ≥ 10% and in 3 - < 10% of patients treated with Mycophenolate Mofetil in adults when used in combination with Cyclosporine and Corticosteroids

Body System	**Adverse Events Reported in Both Renal Transplant Patients (n=991)***	**Adverse Events Reported in Cardiac Transplant Patients Only (n=289)****	**Adverse Events Reported in Hepatic Transplant Patients (n=277)*****
Body as a Whole			
≥10%	Asthenia, fever, headache, infection, pain (includes abdominal, back, and chest), edema, sepsis	Asthenia, fever, chills, headache, infection, pain (includes abdominal, back, and chest), edema, sepsis	Ascites, asthenia, chills, enlarged abdomen, fever, headache, hernia, infection, pain (includes abdominal, back and chest), edema, peritonitis, sepsis
3-<10%	Cysts (including lymphocele and hydrocele), enlarged abdomen, facial edema, flu syndroma, hemorrhage, hernia, malaise, pelvic pain	Cellulitis, cysts (including lymphocele and hydrocele), enlarged abdomen, facial edema, flu syndrome, hemorrhage, hernia, malaise, neck pain, pallor, pelvic pain	Abscess, cellulitis, cyst (including lymphocele and hydrocele) flu syndrome, hemorrhage, malaise, neck pain
Blood and Lymphatic			
≥10%	Anemia (including hypochromic anemia),	Anemia (including hypochromic	Anemia (including hypochromic anemia),

	leucocytosis, leucopenia, thrombocytopenia	anemia), ecchymosis, leycocytosis, leucopenia, thrombocytopenia	leucocytosis, leucopenia, thrombocytopenia
3-<10%	Ecchymosis, polycythemia	Petechia, prothrombin time increased, thromboplastin time increased	Ecchymosis, pancytopenia, prothrombin time increased
Urogenital			
≥10%	Hematuria, renal tubular necrosis, urinary tract infection	Abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection	Abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection
3-<10%	Albuminuria, dysuria, hydronephrosis, impotence, pyelonephritis, urinary frequency	Dysuria, hematuria, impotence, nocturia, renal failure, urinary frequency, urinary incontinence, urinary retention	Acute renal failure, dysuria, hematuria, renal failure, scrotal edema, urinary frequency, urinary incontinence
Cardio vascular			
≥10%	Hypertension	Arrhythmia, bradycardia, cardiac failure, hypertension, hypotension, pericardial effusion	Hypertension, hypotension, tachycardia
3-<10%	Angina pectoris, atrial fibrillation, hypotension, postural hypotension, tachycardia, thrombosis, vasodilation	Angina pectoris, arrhythmias (including supraventricular and ventricular extrasystoles, atrial flutter, suproventricular and ventricular tachycardias), atrial fibrillation, cardiac arrest, congestive	Arterial thrombosis, atrial fibrillation, arrhythmia, bradycardia, vasodilatation, syncope

		heart failure, postural hypotension, pulmonary hypertension, syncope, vasospasm, venous pressure increased	
Metabolic/ Nutritional			
≥10%	Hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hypophosphatemia	Acidosis (metabolic or respiratory), bilirubinemia, elevated BUN, elevated creatinine, elevated enzyme levels (lactic dehydrogenase, SGOT and SGPT), hypercholeterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypervolemia, hypokalemia, hypomagnesemia, hyponatremia, weight gain	Bilirubinemia, elevated BUN, elevated creatinine, healing abnormal, hyperglycemia, hyperkalemia, hypocalcemia, hypokalemia, hypoglycemia, hypomagnesemia, hypophosphatemia, hypoproteinemia
3-<10%	Acidosis (metabolic or respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (gamma glutaryl transpeptidase, lactic dehydrogenase, SGOT, SGPT), elevated creatinine, hypercalcemia, hyperlipimia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, hyperuricemia, weight gain	Abnormal healing, alkaline phosphatase increased, alkalosis, dehydration, gout, hypocalcemia, hypocloremia, hypoglycemia, hypoproteinemia, hypophosphatemia, hypovolemia, hypoxia, respiratory acidosis, thirst, weight loss	Acidosis (metabolic or respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (SGOP and SGPT), hypercholesterolemia, hyperlipemia, hyperphosphatemia, hypervolemia, hyponatremia, hypoxia, hypovolemia, weight gain, weight loss

Gastro-intestinal			
≥10%	Constipation, diarrhea, dyspepsis, nausea and vomiting, oral moniliasis	Constipation, diarrhea, dyspepsis, flatulence, nausea and vomiting, oral moniliasis	Elevated liver function tests (incl. AST, ALT), anorexia, cholangitis, cholestatic jaundice, constipation, diarrhea, dyspepsia, flatulence, hepatitis, nausea and vomiting, oral moniliasis
3-<10%	Elevated liver function tests (incl. AST, ALT), anorexia, flatulence, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, esophagitis, stomatitis	Elevated liver function tests (incl. AST, ALT), anorexia, dysphagia, gastroenteritis, gingivitis, gum hyperplasia, jaundice, melena, esophagitis, stomatitis	Dysphagia, gastritis, gastrointestinal hemorrhage, ileus, jaundice, melaena, mouth ulceration, esophagitis, rectal disorder, stomach ulcer
Respiratory			
≥10%	Cough, increased dyspnea, pharyngitis, pneumonia, bronchitis	Asthma, cough increased, dyspnea, pharyngitis, pleural effusion, pneumonia, rhinitis, sinusitis	Atelectasis, cough increased, dyspnea, pharyngitis, pleural effusion, pneumonia, sinusitis
3-<10%	Asthma, pleural effusion, pulmonary edema, rhinitis, sinusitis	Apnea, atelectasis, bronchitis, epistaxis, hemoptysis, hiccough, neoplasm, pneumothorax, pulmonary edema, sputum increased, voice alteration	Asthma, bronchitis, epistaxis, hyperventilation, pneumothorax, pulmonary edema, respiratory moniliasis, rhinitis
Skin and Appendages			
≥10%	Acne, herpes simplex	Acne, herpes simplex, herpes zoster, rash	Pruritus, rash, sweating

3-<10%	Alopecia, benign neoplasm of skin, fungal dermatitis, herpes zoster, hirsutism, pruritus, skin carcinoma, skin hypertrophy (incl. actinic keratosis), sweating, skin ulcer, rash	Benign neoplasm of skin, fungal dermatitis, hemorrhage, pruritus, skin carcinoma, skin hypertrophy, skin ulcer,sweating	Acne, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, hirsutism, skin benign neoplasm, skin ulcer, vesiculobullous rash
Nervous			
≥10%	Dizziness, insomnia, tremor	Agitation, anxiety, confusion, depression, dizziness, hypertonia, insomnia, paresthesia, somnolence, tremor	Anxiety, confusion, depression, dizziness, insomnia, paresthesia, tremor
3-<10%	Anxiety, depression, hypertonia, paresthesia, somnolence	Convulsion, emothional lability, hallucinations, neuropathy, thinking abnormal, vertigo	Agitation, convulsion, delirium, dry mouth, hypertonia, hypesthesia, neuropathy, psychosis, somnolence, thinking abnormal
Musculo-Skeletal			
≥10%	-	Leg cramps, myalgia, myasthenia	-
3-<10%	Arthralgia, leg cramps, myalgia, myasthenia	Arthralgia	Arthralgia, leg cramps, myalgia, myasthenia, osteoporosis
Special Senses			
≥10%	-	Amblyopia	-
3-<10%	Amblyopia. Cataract, conjunctivitis	Abnormal vision, conjunctivitis,	Abnormal vision, ambylopia,

		deafness, ear pain, eye hemorrhage, tinnitus	conjunctivitis, deafness
Endocrine			
≥10%	-	-	-
3-<10%	Diabetes mellitus, parathyroid disorder (elevated PTH level)	Diabetes mellitus, Cushing's syndrome, hypothyroidism	Diabetes mellitus

***(total n=1483) **(total n=578) ***(total n=564)**

In the three controlled trials for prevention of renal transplant rejection, patients receiving 2 g per day of Mycophenolate Mofetil demonstrated an overall better safety profile than did patients receiving 3 g Mycophenolate Mofetil.

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 postmarketing are described below with the frequencies reported within brackets if known.

Gastrointestinal:

Gingival hyperplasia (≥1/100 to <1/10), colitis including cytomegalovirus colitis, (≥1/100 to <1/10), pancreatitis, (≥1/100 to <1/10) and intestinal villous atrophy.

Disorders related to immunosuppression:

Serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Mycophenolate Mofetil.

Agranulocytosis (≥1/1000 to <1/100) and neutropenia have been reported; therefore, regular monitoring of patients taking Mycophenolate Mofetil is advised. There have been reports of aplastic anaemia and bone marrow depression in patients treated with Mycophenolate Mofetil, some of which have been fatal.

Blood and lymphatic system disorder:
Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with Mycophenolate Mofetil in combination with other immunosuppressive agents.

Hypersensitivity:

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

Pregnancy, puerperium and perinatal conditions

Cases of spontaneous abortions have been reported in patients exposed to Mycophenolate Mofetil, mainly in the first trimester.

Congenital disorders:

Congenital malformations have been observed post marketing in children of patients exposed to Mycophenolate Mofetil in combination with other immunosuppressants,.

Respiratory, thoracic and mediastinal disorders:

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with Mycophenolate Mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders:

Hypogammaglobulinaemia has been reported in patients receiving Mycophenolate Mofetil in combination with other immunosuppressants.

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. If neutropenia develops, dosing with Mycophenolate Mofetil should be interrupted or the dose reduced.

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug.

Storage Conditions

Do not store above 30°C.

Dosage forms or presentation

Mycofit 250 is packed in PVC/PVdC - Alu Blister Pack of 10 capsules. Each printed carton contains 10 such blisters.

Name and address of product registrant

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Date of revision of package insert

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