

Mycophenolate Mofetil can cause first trimester pregnancy loss (miscarriage) and birth defects when used along with other medicines used to prevent organ rejection. Taking Mycophenolate Mofetil while pregnant can harm your unborn baby. Mycophenolate Mofetil suppresses your immune system. This can make you more likely to get infections and certain cancers, such as lymphoma. Mycophenolate Mofetil will be prescribed to you by a doctor with experience in medicines used to prevent organ rejection. See warning and precautions

1. NAME OF THE MEDICINAL PRODUCT

Mycomof 500 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:

Mycophenolate Mofetil.....500 mg

3. PHARMACEUTICAL FORM

Film-coated tablets

Lavender colored capsule shaped tablets, Debossed "500" on one side and "M" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology & Method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Use in renal transplant

Adults:

Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Pediatric population aged 2 to 18 years:

The recommended dose of Mycophenolate Mofetil is 600 mg/m2 administered orally twice daily (up to a maximum of 2 g daily). Tablets should only be prescribed to patients with a body surface area greater than 1.5 m2, at a dose of 1 g twice daily (2 g daily dose).As some adverse reactions occur with greater frequency in this age group compared with adults, temporary dose reduction or interruption may be required as per recommendation. (See dose Modification)

Pediatric population < 2 years

There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

Use in cardiac transplant

Adults:

Treatment 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).

Pediatric population

No data are available for pediatric cardiac transplant patients

Use in special populations

Elderly:

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Renal impairment:

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m2), 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. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

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; dosage reduction or interruption of Mycophenolate Mofetil is not required. There is no basis for dose adjustment of Mycophenolate Mofetil following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Pediatric population

No data are available for treatment of first or refractory rejection in pediatric transplant patients.

Method of administration

For oral use.

Precautions to be taken before handling or administering the medicinal product.

Because Mycophenolate Mofetil has demonstrated teratogenic effects in rats and rabbits, tablets should not be crushed.

4.3 Contraindications

- Mycophenolate Mofetil should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section.
- Hypersensitivity reactions to Mycophenolate Mofetil have been observed (see section 4.8).
- Mycophenolate Mofetil should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Mycophenolate Mofetil treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Mycophenolate Mofetil should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Mycophenolate Mofetil not be given to women who are breastfeeding.

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including are Mycophenolate Mofetil at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8).

Infections

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). 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. There have been published reports of bronchiectasis in adults and children who received Mycophenolate Mofetil in combination with other immunosuppressants. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8).

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 x 103/μl), 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. PRCA may resolve with dose reduction or cessation of therapy. (See section 4.8) 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 as recommended in guidelines.

Gastro-intestinal system

Mycophenolate Mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage and perforation. Mycophenolate 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 (Mycophenolic Acid) enterohepatic recirculation, e.g., ciclosporin, to others devoid of this effect, e.g., tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. (see also section 4.5.). 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 hemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (overall rate of 23% to 27%) have been reported following Mycophenolate Mofetil exposure during pregnancy. Therefore, Mycophenolate Mofetil is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks.

Contraception

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.

4.5 Interaction with other medicinal products and other forms of interaction

Acyclovir

Higher acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir in comparison to the administration of acyclovir alone. Because MPAG (the phenolic glucuronide of MPA) plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate mofetil and acyclovir, or its produgs, 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 aluminum hydroxides, and PPIs, were administered with Mycophenolate mofetil. Data suggests that there is no significant difference seen in transplant rejection rates or rates of graft loss between Mycophenolate Mofetil patients taking PPIs versus patients taking Mycophenolate Mofetil not taking PPIs.

Medicinal products that interfere with enterohepatic recirculation (e.g., cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of Mycophenolate Mofetil.

Cholestyramine

Caution should be used during concomitant administration because of the potential to reduce efficacy of Mycophenolate.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by Mycophenolate Mofetil. In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30% should be expected. 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.

Ciprofloxacin or 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. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

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.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g., isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with Mycophenolate Mofetil.

Isavuconazole

An increase of MPA exposure (AUC_{0-∞}) by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and Mycophenolate Mofetil resulted in an approximately 30% decrease of MPA concentrations.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral Mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of Mycophenolate Mofetil and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increased concentrations in MPA and ganciclovir. No substantial alteration of MPA pharmacokinetics is anticipated and Mycophenolate Mofetil dose adjustment is not required.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of Mycophenolate Mofetil.

Rifampicin

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

It is recommended, however, to administer Mycophenolate Mofetil at least one hour before or three hours after sevelamer intake to minimize the impact on the absorption of MPA. There are no data on Mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus

In renal transplant patients, tacrolimus concentration did not appear to be altered by Mycophenolate Mofetil.

Live vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

Pediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking Mycophenolate Mofetil must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting Mycophenolate therapy, during therapy, and for six weeks after stopping the therapy.

Pregnancy

Mycophenolate Mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatmnet should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3). Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy. Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital

Breast-feeding

Mycophenolate Mofetil is contraindicated in nursing mothers (see section 4.3).

Men

The limited clinical evidence available does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil. The following precautionary measures are recommended:

Fertility

Mycophenolate Mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first-generation offspring in the absence of maternal toxicity.

4.7 Effects on ability to drive and use machines

Mycophenolate Mofetil has a moderate influence on the ability to drive and use machines.

It may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhea (up to 52.6%), leucopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) are among the most common and/or serious adverse reactions associated with the administration of Mycophenolate Mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections (see section4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: 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) and very rare (<1/10,000). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Adverse reaction (MedDRA) System Organ Class	Renal transplant	Hepatic transplant	Cardiac transplant
	Frequency	Frequency	Frequency
Infections and infestations			
Bacterial infections	Very Common	Very Common	Very Common
Fungal infections	Common	Very Common	Very Common
Protozoal infections	Uncommon	Uncommon	Uncommon
Viral infections	Very Common	Very Common	Very Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Common	Common	Common
Lymphoma	Uncommon	Uncommon	Uncommon
Lymphoproliferative	Uncommon	Uncommon	Uncommon
Disorder	Common	Common	Common
Skin cancer	Common	Uncommon	Common
Blood and lymphatic system disorders			
Anemia	Very Common	Very Common	Very Common
Aplasia pure red cell	Uncommon	Uncommon	Uncommon
Bone marrow failure	Uncommon	Uncommon	Uncommon
Echymosis	Common	Common	Very Common
Leukocytosis	Common	Very Common	Very Common
Leucopenia	Very Common	Very Common	Very Common
Pancytopenia	Common	Common	Uncommon
Pseudo lymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	Very Common	Very Common
Metabolism and nutrition disorders			
Acidosis	Common	Common	Very Common
Hypercholesterolemia	Very Common	Common	Very Common
Hyperglycemia	Common	Very Common	Very Common
Hyperkalemia	Common	Very Common	Very Common
Hyperlipidemia	Common	Common	Very Common
Hypocalcemia	Common	Very Common	Common
Hypokalemia	Common	Very Common	Very Common
Hypomagnesemia	Common	Very Common	Very Common
Hypophosphatemia	Very Common	Very Common	Common
Hyperuricemia	Common	Common	Very Common

Gout	Common	Common	Very Common
Weight decreased	Common	Common	Common
Psychiatric Disorders			
Confusional state	Common	Very Common	Very Common
Depression	Common	Very Common	Very Common
Insomnia	Common	Very Common	Very Common
Agitation	Uncommon	Common	Very Common
Anxiety	Common	Very Common	Very Common
Thinking abnormal	Uncommon	Common	Common
Nervous system disorders			
Dizziness	Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common
Hypertonia	Common	Common	Very Common
Paresthesia	Common	Very Common	Very Common
Somnolence	Common	Common	Very Common
Tremor	Common	Very Common	Very Common
Convulsion	Common	Common	Common
Dysgeusia	Uncommon	Uncommon	Common
Cardiac disorders			
Tachycardia	Common	Very Common	Very Common
Vascular disorders			
Hypertension	Very Common	Very Common	Very Common
Hypotension	Common	Very Common	Very Common
Lymphocele	Uncommon	Uncommon	Uncommon
Venous thrombosis	Common	Common	Common
Vasodilatation	Common	Common	Very Common
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis	Uncommon	Uncommon	Uncommon
Cough	Very Common	Very Common	Very Common
Dyspnea	Very Common	Very Common	Very Common
Interstitial lung disease	Uncommon	Very Rare	Very Rare
Pleural effusion	Common	Very Common	Very Common
Pulmonary fibrosis	Very Rare	Uncommon	Uncommon
Gastrointestinal disorders			
Abdominal distension	Common	Very Common	Common
Abdominal pain	Very Common	Very Common	Very Common
Colitis	Common	Common	Common
Constipation	Very Common	Very Common	Very Common
Decreased appetite	Common	Very Common	Very Common
Diarrhea	Very Common	Very Common	Very Common
Dyspepsia	Very Common	Very Common	Very Common
Esophagitis	Common	Common	Common
Eructation	Uncommon	Uncommon	Common
Flatulence	Common	Very Common	Very Common
Gastritis	Common	Common	Common
Gastrointestinal hemorrhage	Common	Common	Common

Gastrointestinal ulcer	Common	Common	Common
Gingival hyperplasia	Common	Common	Common
Ileus	Common	Common	Common
Mouth ulceration	Common	Common	Common
Nausea	Very Common	Very Common	Very Common
Pancreatitis	Uncommon	Common	Uncommon
Stomatitis	Common	Common	Common
Vomiting	Very Common	Very Common	Very Common
Immune system disorders			
Hypersensitivity	Uncommon	Common	Common
Hypogammaglobulinemia	Uncommon	Very Rare	Very Rare
Hepatobiliary disorders			
Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very Common
Hepatic enzyme increased	Common	Very Common	Very Common
Hepatitis	Common	Very Common	Uncommon
Hyperbilirubinemia	Common	Very Common	Very Common
Jaundice	Uncommon	Common	Common
Skin and subcutaneous tissue disorders			
Acne	Common	Common	Very Common
Alopecia	Common	Common	Common
Rash	Common	Very Common	Very Common
Skin hypertrophy	Common	Common	Very Common
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Common	Very Common
Muscular weakness	Common	Common	Very Common
Renal and urinary disorders			
Blood creatinine increased	Common	Very Common	Very Common
Blood urea increased	Uncommon	Very Common	Very Common
Hematuria	Very Common	Common	Common
Renal impairment	Common	Very Common	Very Common
General disorders and administration site conditions			
Asthenia	Very Common	Very Common	Very Common
Chills	Common	Very Common	Very Common
Oedema	Very Common	Very Common	Very Common
Hernia	Common	Common	Rare
Malaise	Common	Common	Common
Pain	Common	Very Common	Very Common
Pyrexia	Very Common	Very Common	Very Common
De novo purine synthesis inhibitors associated acute inflammatory syndrome	Uncommon	Uncommon	Uncommon

Description of selected adverse reactions

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).

Infections
All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections observed are sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection.

Blood and lymphatic disorders
Cytopenias, including leucopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with Mycophenolate Mofetil and may lead or contribute to the occurrence of infections and hemorrhages (see section 4.4). Agranulocytosis 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 anemia and bone marrow

failure in patients treated with Mycophenolate Mofetil some of which have been fatal. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Mycophenolate (see section 4.4).

Gastrointestinal disorders
The most serious gastrointestinal disorders were ulceration and hemorrhage which are known risks associated with Mycophenolate mofetil. Mouth, esophageal, gastric, duodenal and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials, (see section 4.4)

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

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

General disorders
Oedema, including peripheral, face and scrotal oedema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

Special populations
Pediatric population
The type and frequency of adverse reactions in a clinical study, which recruited 92 pediatric patients aged 2 to 18 years who were given 600 mg/m2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g Mycophenolate Mofetil twice daily. However, the following treatment-related adverse events were more frequent in the pediatric population, particularly in children under 6 years of age, when compared to adults: diarrhea, sepsis, leucopenia, anemia and infection.

Elderly
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 hemorrhage and pulmonary oedema, compared to younger individuals.

4.9 Overdose
It is expected that an overdose of mycophenolate mofetil could possibly result in over suppression 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. Hemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acidsequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug.

5. PHARMACOLOGICAL PROPERTIES
Absorption
Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, MPA. Food had no effect on the extent of absorption (MPA AUC) of Mycophenolate Mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

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.

Biotransformation
MPA is metabolized 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 (diarrhea, leucopenia)

Elimination
A negligible amount of substance is excreted as MPA (< 1% of the dose) in the urine. Oral administration of radio labelled 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 feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

Special populations
Renal impairment
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
Studies have shown that dose adjustment of Mycophenolate Mofetil does not appear to be necessary.

Hepatic impairment
Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect on hepatic MPA glucuronidation processes.

Pediatric population
Pharmacokinetic parameters were evaluated in 49 pediatric renal transplant patients (aged 2 to 18 years) given 600mg/m2 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
The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (>= 65 years) when compared to younger transplant patients.

Patients taking oral contraceptives
A study done on women have shown that the pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of Mycophenolate Mofetil.

5.3 Preclinical safety data
In experimental models, mycophenolate mofetil was not tumorigenic. 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. Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity. The hematopoietic 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.

6. PHARMACEUTICAL PARTICULARS
6.1 Pack Size
For 500mg tablets:
4x 10's (40) tablets.
6.2 Storage Conditions
Do not store above 30°C, Protect from sunlight and moisture.

6.3 Dosage and Instructions
As directed by Physician. Keep out of reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایت: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

For adverse event reporting, kindly email us at
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7. MANUFACTURER

Manufactured by:
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