Mycophenolate Mofetil

Mofilet - 500

500 mg
Film Coated Tablets
Immunosuppressant

FORMULATION :
Each film coated tablet contains:
Mycophenolate Mofetil 500 mg
Excipients q.s.

DESCRIPTION :
Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase (IMPDH) inhibitor. Chemically MMF is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, and a molecular weight of 433.50

CLINICAL PHARMACOLOGY :
Mechanism of Action: In the body, Mycophenolate mofetil is hydrolyzed to form MPA, which is the active metabolite. Mycophenolic acid is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), 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 utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. MMF does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but blocks the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetics : Mycophenolate mofetil is rapidly and completely absorbed orally. Bioavailability of Mycophenolic acid is 94%. After administration of single dose of Mycophenolate mofetil in the fasting state, the maximum plasma concentration (C_{max}) of 3.67 ± 0.51 mcg/ml was achieved in 2.92 ± 0.79 hrs (T_{max}). The plasma elimination half life (t1/2) of Mycophenolate mofetil was found to be 11.74 ± 3.29 hrs. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.
Mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic recirculation. Negligible amount of drug is excreted as MPA in the urine. Most of the orally administered dose is excreted in the urine as MPAG.

INDICATIONS :
For prophylaxis of renal graft rejection, cardiac graft rejection & rejection in hepatic transplantation. Mycophenolate should be used concomitantly with cyclosporine and corticosteroids.

DOSAGE AND ADMINISTRATION :
Renal transplantation: A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in adult patients.
Cardiac transplantation: A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.
Hepatic transplantation: A dose 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.
Food has no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. It is recommended that Mycophenolate be administered on an empty stomach. However, in stable renal transplant patients, MMF may be administered with food if necessary.

ADVERSE EFFECTS :
The principal adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections. Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.
Other adverse reactions reported in combination with cyclosporine and corticosteroids, are as follows:
Cardiovascular : Angina pectoris, atrial fibrillation, hypotension, palpitation, peripheral vascular disorder, postural hypotension, tachycardia, thrombosis, vasodilation, ventricular extrasystole, CHF, supraventricular tachycardia, ventricular tachycardia, atrial flutter, pulmonary hypertension, heart arrest, increased venous pressure, syncope, supraventricular extrasystoles, pallor, vasospasm.
CNS : Anxiety, depression, hypertonia, paresthesia, somnolence, emotional lability, neuropathy, convulsion, hallucinations, abnormal thinking, vertigo.
Dermatologic : Alopecia, fungal dermatitis, hirsutism, pruritus, benign skin neoplasm, skin disorder, sweating, hemorrhage, skin carcinoma.
Endocrine : Diabetes, parathyroid disorder, Cushing's syndrome, and hypothyroidism.
Gastrointestinal : Anorexia, esophagitis, flatulence, gastritis, gastroenteritis, GI hemorrhage, gingivitis, gum hyperplasia, hepatitis, ileus, infection, mouth ulceration; rectal disorder, liver damage, dysphagia, jaundice, stomatitis, thirst.
Urogenita : Albuminuria, dysuria, hydronephrosis, impotence, pain, pyelonephritis, urinary frequency, nocturia, kidney failure, urine abnormality, hematuria, urinary incontinence, prostatic disorder, urinary retention.
Musculoskeletal : Arthralgia, joint disorder, leg cramps myalgia, myasthenia.
Respiratory : Asthma, lung edema, pleural effusion, rhinitis, sinusitis, atelectasis, hiccough, pneumothorax, increased sputum, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasm, respiratory acidosis.
Special sense : Amblyopia, cataract, conjunctivitis, ear pain, deafness, ear disorder, tinnitus, abnormal vision, lacrimation disorder, eye hemorrhage.
Miscellaneous : Abdomen enlarged, chills/fever, cyst, face edema, flu syndrome, hemorrhage, hernia, malaise, pelvic pain, ecchymosis, polycythemia, neck pain, cellulitis, increased prothrombin, decreased thromboplastin, petechia, phlebitis, thrombosis, weight gain/loss, abnormal healing dehydration.
Lab test abnormalities : Increased alkaline phosphatase, creatinine, gamma glutamyl transpeptidase, lactic dehydrogenase, AST and ALT, hypercalcemia, hyperlipemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, acidosis, hypoxia, hypophosphatemia, alkalosis, hypochloremia.

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DRUG INTERACTIONS :
Acyclovir: Co-administration of MMF and acyclovir resulted in no significant change in Mycophenolic acid AUC and C_{max}. However, MPAG and acyclovir plasma AUCs can increase. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two drugs to compete for tubular secretion, further increasing the concentrations of both drugs.
Antacids with Magnesium and Aluminum hydroxides : Absorption of a single dose of Mycophenolate mofetil is decreased when administered with antacids containing magnesium and aluminium hydroxides. Mycophenolate mofetil may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that mycophenolate mofetil and the antacid not be administered simultaneously
Cholestyramine : Mycophenolate mofetil is not recommended to be given with cholestyramine or other agents that may interfere with entero-hepatic recirculation as AUC of Mycophenolic acid is decreased.
Ganciclovir : Since MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which Mycophenolate mofetil and ganciclovir are co-administered, patients should be monitored carefully.
Oral Contraceptives : Mycophenolate mofetil may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives be co-administered with Mycophenolate mofetil with caution and additional birth control methods be considered.
Live Vaccines : During treatment with Mycophenolate mofetil, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations might be less effective.
Azathiprine : It is recommended that Mycophenolate mofetil not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

WARNINGS AND PRECAUTIONS :
Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolate mofetil, as part of an immunosuppressive regimen 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. Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.
Lymphoproliferative disease or lymphoma developed in patients receiving Mycophenolate mofetil (2 or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients.
Severe neutropenia may develop in renal transplant patients receiving mycophenolate mofetil 3 g daily. Patients receiving Mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to Mycophenolate mofetil itself, concomitant medications, viral infections, or combination of these causes. If neutropenia develops, dosing with Mycophenolate mofetil should be interrupted or the dose is reduced, appropriate diagnostic tests are performed, and the patient is managed appropriately.
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.
Gastrointestinal bleeding (requiring hospitalization) has been observed in renal transplant patients treated with Mycophenolate mofetil.
Subjects with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2) receiving single doses of Mycophenolate mofetil may shows higher plasma MPA and MPAG AUCs. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of Mycophenolate mofetil greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed.
Carcinogenesis, mutagenesis, and impairment of fertility : Mycophenolate mofetil is not tumorigenic in rat and mice studies. Mycophenolate mofetil is genotoxic in the mouse lymphoma/thymidine kinase assay and the in vivo mouse micronucleus assay but is not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay. Mycophenolate mofetil has no effect on fertility in rats.
Pregnancy : Category D. This product is not recommended during pregnancy. Women of child bearing potential must use effective contraception 4 weeks prior to and 6 weeks after stopping therapy, and have a negative serum or urine pregnancy test within 1 week prior to beginning therapy. This product may decrease the blood levels of the hormones in the oral contraceptive pill and theoretically reduce its effectiveness.
Nursing Mothers : Studies in rats treated with Mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

CONTRAINDICATIONS :
Mycophenolate mofetil is contraindicated in patients with a hypersensitivity to Mycophenolate mofetil, mycophenolic acid or any component of the drug product.

OVERDOSAGE :
There has been no reported experience of overdose of Mycophenolate mofetil in humans. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of Mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine.

STORAGE CONDITIONS: Store at temperatures not exceeding 30°C.
Keep in a dry and dark place.
CAUTION : Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
PRESENTATION : Alu/Alu blister pack x 10's (box of 10's).
Keep all medicines out of reach of children.
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Reg. No: DR - XY37648
Date of Renewal of Authorization: 23 October 2020

Manufactured by :
Emcure
PHARMACEUTICALS LIMITED
Hinjawadi, Pune - 411 057, India.

Imported & Distributed by:
Macropharma Corporation
90 Upper Gondola, San Francisco Village, Muzon, Taytay, Rizal
Date of revision of package insert: Aug. 2022

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Product	Mofilet - 500	**New / Revised A/W**	Revised A/W	**FDA Lic. Availability**	Avail.
Dosage form	Tablet	**Colour Scheme**	Black	**Proof 1**	08.08.2022
Therapeutic Category	Immunosuppressant	**Pantone Shades**	N.A.	**Corrections of Proof 1**	Editorial changes
Item	Philipines Export Pack Insert A/W	**Total No. of Colours**	4	**Proof 2**	10.08.2022
Dimension	L.80 x H. 210 mm (Folded 80 x 27 mm)	**Special Effect (if any)**	N.A.	**Corrections of Proof 2**	
Substrate	Super white maplitho paper	**Item Code**	514444233PH02	**Proof 3**	
Specification	60 GSM	**Marketing Division**	Emcure Export	**Corrections of Proof 3**	
Printing Area	B/B	**Design / Colour Approved on**	At the time of launching	**Final**	
Item Style	N.A.	**Vendor**		**A/W Checked by**	PMD Cell
A/W Proportion	Same Size	**Country**	Philipines Export	**A/W Verified by**	Production / QC
Product Status	Emcure Own Jammu Unit			**A/W Approved by**	Unit Head
Remark (If any) : Remark-change in importer address					