ANNEX – 3

Copy of proposed Package Insert, label and carton

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Rx Mycophenolate Mofetil Tablets IP 250 mg / 500 mg

WARNING : EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS
Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe mycophenolate mofetil. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Composition :
Each film coated tablet contains :
Mycophenolate Mofetil IP 250 mg
Excipients q.s.
Colours : Black Oxide of Iron & Titanium Dioxide IP

Composition :
Each film coated tablet contains :
Mycophenolate Mofetil IP 500 mg
Excipients q.s.
Colours : Red Oxide of Iron & Titanium Dioxide IP

DESCRIPTION
Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase (IMPDH) inhibitor. Chemically MMF is 2- orpholinoethyl (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, MMF 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: MPA is rapidly and completely absorbed orally. Bioavailability of MPA is 94%. The mean (±SD) apparent volume of distribution of MPA is approximately 4.0 (±1.2) L/kg following oral administration. Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.
MMF 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
The preparation shall be indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogenic renal transplants increased graft, patients survival receiving allogenic cardiac transplants, and in patients receiving allogenic hepatic Transplantation use concomitantly with cyclosporin 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 MMF be administered on an empty stomach. However, in stable renal transplant patients, MMF may be administered with food if necessary.

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

WARNINGS AND PRECAUTIONS
Lymphoma and malignancy: Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, 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.

Infections: Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Latent viral infections: Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including MMF.
In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.
BKVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Neutropenia: Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or combination of these causes. If neutropenia develops, dosing with MMF should be interrupted or the dose is reduced, appropriate diagnostic tests are performed, and the patient is managed appropriately. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.
Pure red cell aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Gastrointestinal disorder: Gastrointestinal bleeding (requiring hospitalization) has been observed in patients treated with MMF. Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active serious digestive system disease.

Patients with HGPRT deficiency: On theoretical grounds, because MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Immunizations: During treatment with MMF, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

Contraception: Females of reproductive potential must use acceptable birth control during entire MMF therapy and for 6 weeks after stopping MMF, unless the patient chooses to avoid heterosexual intercourse completely (abstinence).

Laboratory tests: Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

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:

General: Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, ascites, enlarged abdomen, abscess, accidental injury, cellulitis, chills with fever, facial oedema, hemorrhage, hernia, laboratory test abnormality, malaise, neck pain, pelvic pain, peritonitis.
Hematologic and lymphatic: Anemia, leukopenia, thrombocytosis, hypochromic anemia, leukocytosis, coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.
Cardiovascular : Hypertension, hypotension, cardiac disorders, tachycardia, 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 extrasystole, pallor, vasospasm.
Metabolic and nutritional: Peripheral oedema, hypercholesterolemia, hypokalemia, hyperkalemia, hyperglycemia, increased creatinine, increased BUN, increased lactate dehydrogenase levels, hypomagnesemia, hypocalcemia.

VPG
210319

Front

CNS: Tremors, insomnia, dizziness, 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: Diarrhoea, constipation, nausea, dyspepsia, anorexia, esophagitis, flatulence, gastritis, gastroenteritis, GI hemorrhage, gingivitis, gum hyperplasia, hepatitis, ileus, infection, mouth ulceration, rectal disorder, liver damage, dysphagia, jaundice, stomatitis, thirst.
Urogenital: Urinary tract infection, kidney function abnormal, 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: Infection, dyspnoea, cough increased, sinusitis, asthma, lung edema, pleural effusion, rhinitis, sinusitis, atelectasis, hiccough, pneumothorax, increased sputum, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasm, respiratory acidosis.
Skin and appendages: Rash.
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.

DRUG INTERACTIONS
Acyclovir: Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids with magnesium and aluminum hydroxides: MMF may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that MMF and the antacid not be administered simultaneously.
Proton pump inhibitors: Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving has been reported to reduce the exposure to mycophenolic acid (MPA). The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with MMF.

Cholestyramine: Cholestyramine has been found to reduce MPA AUC by approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of MMF. Therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine: In renal transplant patients, mean MPA exposure (AUC_{0-12h}) was approximately 30-50% greater when MMF is administered without cyclosporine compared with when MMF is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

Gancyclovir: No pharmacokinetic interaction has been observed between gancyclovir and MMF. Because 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 MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

Oral contraceptives: MMF may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister MMF with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used.

Sevelamer: Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C_{max} and AUC_{0-12h}. This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with MMF. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after MMF intake to minimize the impact on the absorption of MPA.

Trimethoprim and sulfamethoxazole: Trimethoprim 800 mg/ sulfamethoxazole 160 mg has not been found to affect bioavailability of MMF.

Norfloxacin and metronidazole: Following single dose administration of MMF, the mean MPA AUC_{0-48h} was significantly reduced compared to the administration of mycophenolate mofetil alone. MMF is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA AUC_{0-48h} when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately.

Ciprofloxacin and amoxicillin plus clavulanic acid: Approximately 50% reductions in median trough MPA concentrations (predose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

Rifampicin: In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure (AUC_{0-12h}) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, MMF is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

Azathioprine: It is recommended that MMF 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.

Other interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion. Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

USE IN SPECIAL POPULATION
Pregnancy: Pregnancy Category D. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing mothers: Studies in rats treated with MMF 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 MMF, 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.

Geriatric use: Clinical studies of MMF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals.

Renal impairment: Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of MMF showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of MMF greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed.
In patients with delayed renal graft function posttransplant, mean MPA $AUC_{(0-12h)}$ was comparable, but MPAG $AUC_{(0-12h)}$ was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. No dose adjustment is recommended for these patients; however, they should be carefully observed.

Patients with hepatic impairment: No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies.

OVERDOSAGE:
There has been no reported experience of overdose of MMF 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 MMF 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 : Store protected from light & moisture, at a temperature not exceeding 30°C.
Presentation : A blister strip of 10 tablets.

Manufactured by :
Emcure
PHARMACEUTICALS LTD.
Lane No. 3, Phase - II, SIDCO,
Bari - Brahmana, Jammu - 181 133, India.

SAPCODE

Back

Product	Mycophenolate Mofetil Tablets IP 250 mg/500 mg	**New / Revised A/W**	New Artwork	**FDA Lic. Availability**	Avail.
Dosage form	Tablets	**Reason for change**	N.A.	**Proof 1**	21.03.2019
Therapeutic Category	Immunosuppressant	**Colour Scheme**	Black	**Corrections of Proof 1**	
Item	Pack insert A/W	**Pantone Shades**	N.A.	**Proof 2**	
Dimension	L. 80 x 250 mm (Folded 80 x 31.5 mm)	**Total No. of Colours**	1	**Corrections of Proof 2**	
Substrate	Super white maplitho paper	**Special Effect (if any)**	N.A.	**Proof 3**	
Specification	60 GSM	**Item Code**	SAPCODE	**Corrections of Proof 3**	
Printing Area	F/F	**Marketing Division**		**Final**	
Item Style	N.A.	**Design / Colour Approved on**	N.A.	**A/W Checked by**	PMD Cell
A/W Proportion	Same Size	**Vendor**		**A/W Verified by**	Production / QC
Product Status	Emcure Own Jammu Unit	**Country**	Domestic	**A/W Approved by**	Unit Head
Remark (If any) : New Artwork					

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Rx Mycophenolate Mofetil Tablets IP 250 mg / 500 mg

WARNING : EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS
Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe mycophenolate mofetil. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Composition :
Each film coated tablet contains :
Mycophenolate Mofetil IP 250 mg
Excipients q.s.
Colours : Black Oxide of Iron & Titanium Dioxide IP

Composition :
Each film coated tablet contains :
Mycophenolate Mofetil IP 500 mg
Excipients q.s.
Colours : Red Oxide of Iron & Titanium Dioxide IP

DESCRIPTION

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase (IMPDH) inhibitor. Chemically MMF is 2- orpholinoethyl (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, MMF 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: MPA is rapidly and completely absorbed orally. Bioavailability of MPA is 94%. The mean (±SD) apparent volume of distribution of MPA is approximately 4.0 (±1.2) L/kg following oral administration. Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.
MMF 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

The preparation shall be indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogenic renal transplants increased graft, patients survival receiving allogenic cardiac transplants, and in patients receiving allogenic hepatic Transplantation use concomitantly with cyclosporin 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 MMF be administered on an empty stomach. However, in stable renal transplant patients, MMF may be administered with food if necessary.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lymphoma and malignancy: Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, 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.

Infections: Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Latent viral infections: Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including MMF.

In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BKVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Neutropenia: Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or combination of these causes. If neutropenia develops, dosing with MMF should be interrupted or the dose is reduced, appropriate diagnostic tests are performed, and the patient is managed appropriately. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Pure red cell aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Gastrointestinal disorder: Gastrointestinal bleeding (requiring hospitalization) has been observed in patients treated with MMF. Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active serious digestive system disease.

Patients with HGPRT deficiency: On theoretical grounds, because MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Immunizations: During treatment with MMF, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

Contraception: Females of reproductive potential must use acceptable birth control during entire MMF therapy and for 6 weeks after stopping MMF, unless the patient chooses to avoid heterosexual intercourse completely (abstinence).

Laboratory tests: Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

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:

General: Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, ascites, enlarged abdomen, abscess, accidental injury, cellulitis, chills with fever, facial oedema, hemorrhage, hernia, laboratory test abnormality, malaise, neck pain, pelvic pain, peritonitis.

Hematologic and lymphatic: Anemia, leukopenia, thrombocytosis, hypochromic anemia, leukocytosis, coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.

Cardiovascular : Hypertension, hypotension, cardiac disorders, tachycardia, 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 extrasystole, pallor, vasospasm.

Metabolic and nutritional: Peripheral oedema, hypercholesterolemia, hypokalemia, hyperkalemia, hyperglycemia, increased creatinine, increased BUN, increased lactate dehydrogenase levels, hypomagnesemia, hypocalcemia.

CNS: Tremors, insomnia, dizziness, 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: Diarrhoea, constipation, nausea, dyspepsia, anorexia, esophagitis, flatulence, gastritis, gastroenteritis, GI hemorrhage, gingivitis, gum hyperplasia, hepatitis, ileus, infection, mouth ulceration; rectal disorder, liver damage, dysphagia, jaundice, stomatitis, thirst.
Urogenital: Urinary tract infection, kidney function abnormal, 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: Infection, dyspnoea, cough increased, sinusitis, asthma, lung edema, pleural effusion, rhinitis, sinusitis, atelectasis, hiccough, pneumothorax, increased sputum, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasm, respiratory acidosis.
Skin and appendages: Rash.
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.

DRUG INTERACTIONS

Acyclovir: Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids with magnesium and aluminum hydroxides: MMF may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that MMF and the antacid not be administered simultaneously.
Proton pump inhibitors: Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving has been reported to reduce the exposure to mycophenolic acid (MPA). The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with MMF.

Cholestyramine: Cholestyramine has been found to reduce MPA AUC by approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of MMF. Therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine: In renal transplant patients, mean MPA exposure ($AUC_{0\text{-}12h}$) was approximately 30-50% greater when MMF is administered without cyclosporine compared with when MMF is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

Gancyclovir: No pharmacokinetic interaction has been observed between gancyclovir and MMF. Because 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 MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

Oral contraceptives: MMF may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister MMF with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used.

Sevelamer: Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C_{max} and $AUC_{0\text{-}12h.}$ This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with MMF. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after MMF intake to minimize the impact on the absorption of MPA.

Trimethoprim and sulfamethoxazole: Trimethoprim 800 mg/ sulfamethoxazole 160 mg has not been found to affect bioavailability of MMF.

Norfloxacin and metronidazole: Following single dose administration of MMF, the mean MPA $AUC_{0\text{-}48h}$ was significantly reduced compared to the administration of mycophenolate mofetil alone. MMF is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA $AUC_{0\text{-}48h}$ when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately.

Ciprofloxacin and amoxicillin plus clavulanic acid: Approximately 50% reductions in median trough MPA concentrations (predose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

Rifampicin: In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure ($AUC_{0\text{-}12h}$) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, MMF is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

Azathioprine: It is recommended that MMF 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.

Other interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion. Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

USE IN SPECIAL POPULATION

Pregnancy: Pregnancy Category D. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing mothers: Studies in rats treated with MMF 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 MMF, 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.

Geriatric use: Clinical studies of MMF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals.

Renal impairment: Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of MMF showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of MMF greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed.
In patients with delayed renal graft function posttransplant, mean MPA $AUC_{(0\text{-}12h)}$ was comparable, but MPAG $AUC_{(0\text{-}12h)}$ was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. No dose adjustment is recommended for these patients; however, they should be carefully observed.

Patients with hepatic impairment: No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies.

OVERDOSAGE:

There has been no reported experience of overdose of MMF 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 MMF 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 : Store protected from light & moisture, at a temperature not exceeding 30°C.
Presentation : A blister strip of 10 tablets.

Manufactured by :

Emcure

PHARMACEUTICALS LTD.

Lane No. 3, Phase - II, SIDCO,
Bari - Brahmana, Jammu - 181 133, India.

SAPCODE