Prescribing Information (Summary of Product Characteristics)

1. Name of the medicinal Product

Mycophenolate Mofetil Tablets USP 500 mg

2. Qualitative and Quantitative Composition

Qualitative declaration

Mycophenolate Mofetil USP

Quantitative declaration

Excipients with known effect: Ponceau 4R

For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Solid Oral Dosage Form, Tablets

Distribution category: POM

Description: Purple coloured, capsule shape, biconvex, break line on one side and plain on other side film coated tablets.

4. Clinical Particulars

1. Therapeutic Indications

Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate mofetil should be used concomitantly with cyclosporine and corticosteroids.

2. Posology and Method of Administration

Route of administration: Oral

Adult and Geriatrics:

Renal transplant patients: A dose of 1 g taken twice a day (daily dose of 2 g) is recommended after kidney transplantation. In stable renal transplant patients, Mycophenolate mofetil tablets may be administered with food if necessary or as per recommendation from physician.

Cardiac transplant patients: A dose of 1.5 g twice a day (daily dose of 3 g) is recommended after heart transplantation.
Hepatic transplant patients: A dose of 1.5 g taken twice a day (daily dose of 3 g) is recommended after liver transplantation.

Pediatrics (3 months to 18 years of age):
Patients with a body surface area >1.5 m may be administered with mycophenolate mofetil tablets at a dose of 1 g twice daily (2 g daily dose recommended).

Patients with Hepatic Impairment: No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is unknown whether dose adjustments are needed for hepatic disease with other etiologies.

Mycophenolate mofetil tablet should be administered on an empty stomach.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

3. Contraindications

It is contraindicated in patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. It may cause Allergic reactions. It should not be given to women of childbearing potential who are not using highly effective contraception. The treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy. It should not be used during pregnancy unless there

is no suitable alternative treatment to prevent transplant rejection. It should not be given to women who are breastfeeding.

4. Special Warnings and Special Precautions for Use

Warning: Increased susceptibility to infection and possible lymphoma development may result from immunosuppression. Give drug under supervision of physician experienced in immunosuppressive therapy and management of renal, cardiac, or hepatic transplant patients, in facility with adequate diagnostic and treatment resources. Physician responsible for maintenance therapy should have complete information needed for patient follow-up.

Special Note:

Female Patients: Using mycophenolate mofetil in combination with other medicines used to prevent organ rejection while pregnant; may cause early pregnancy loss and infant birth defects. Women must not take mycophenolate mofetil tablets while they are pregnant as it may cause an increased risk of first trimester. It should not be initiated until a negative pregnancy test report is obtained.

Male Patients: Sexually active male patients and/or their female partners are recommended to use effective birth control while taking mycophenolate mofetil tablets. Men should not donate semen during therapy and for 90 days after taking of mycophenolate mofetil tablets.
While taking this tablets, avoid using tanning beds or sunlamps.

Patients should take precautions;

Lymphoma and malignancy: Patients receiving immunosuppressive regimens link combine drugs, 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, lethal infections, and sepsis.

Latent viral infections: increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy which have been observed in patients receiving immunosuppressants. Physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. In such patients reducing the amount of immunosuppression should be given. In transplant patients, physicians should also consider reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Neutropenia: Patients should be monitored for neutropenia. The development of neutropenia may be related to 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. The treatment 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 have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil-induced pure red cell aplasia is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, pure red cell aplasia was found to be reversible with

dose reduction or cessation of mycophenolate mofetil therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Gastrointestinal disorder: Gastrointestinal bleeding has been observed in patients treated with mycophenolate mofetil. Gastrointestinal perforations have rarely been observed. Most patients receiving mycophenolate mofetil 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 mycophenolate mofetil. Because 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 mofetil should be administered with caution in patients with active serious digestive system disease.

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

Immunizations: During treatment with mycophenolate mofetil, 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 mycophenolate mofetil therapy and for 6 weeks after stopping mycophenolate mofetil, 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.

Pregnancy: It should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.

Lactation: It is small amount of drug concentration excreted into human milk. It should not be recommended during breast-feeding.

Caution for use: excipients with known effect: it contains Ponceau 4R: it may cause allergic reaction.

5. Interaction with other medicinal products and other forms of interaction

Acyclovir, antacids with magnesium and aluminum hydroxides, proton pump inhibitors, lansoprazole, pantoprazole, cholestyramine, cyclosporine, gancyclovir, oral contraceptives, birth control pill, transdermal patch, vaginal ring, injection, and implant, sevelamer, trimethoprim and sulfamethoxazole, norfloxacin and metronidazole, ciprofloxacin and amoxicillin plus clavulanic acid: rifampicin: azathioprine, 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.

6. Pregnancy and Lactation

Pregnancy: It should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.

Lactation: It is small amount of drug concentration excreted into human milk. It should not be recommended during breast-feeding.

7. Effects on ability to Drive and use Machines

It 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.

8. Undesirable Effects

Central nerve system: headache, dizziness, insomnia, asthenia, tremor. Cardiovascular: chest pain, hypertension, peripheral edema. Ear, eye, nose, throat: pharyngitis, oral moniliasis. Gastrointestinal: nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, GI hemorrhage. Genital urinary: urinary tract infection, hematuria, renal tubular necrosis. Hematologic: anemia, hypochromic anemia, leukocytosis, leukopenia, thrombocytopenia. Metabolic: hypophosphatemia, hyperglycemia, hypokalemia, hyperkalemia.

Musculoskeletal: back pain. Respiratory: dyspnea, cough, bronchitis, pneumonia.

Skin: acne, rash. Other: pain, fever, opportunistic infections, fatal infections, sepsis, lymphoma and other cancers (especially of skin). Not known: serious side effects: Endocarditis, hypogammaglobulinaemia, malignancy, meningitis, Neutropenia, polyomavirus-associated nephropathy, progressive multifocal leukoencephalopathy, pure red cell aplasia.

9. Overdose

Symptoms: The overdose of mycophenolate mofetil tablets is very limited. The events received from reports of overdose fall within the known safety profile of the drug. If the highest dose administered to renal transplant patients compared to the recommended dose then gastrointestinal intolerance (nausea, vomiting, and/or diarrhea) and occasional hematologic abnormalities may occur. Principally neutropenia, leading to a need to reduce dosing.

Treatment: Principally MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug.

2. Pharmacological Properties

2.1. Pharmacodynamics Properties

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), Inosine monophosphate dehydrogenase (IMPDH) inhibitor which Inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines. MPA inhibits proliferative responses of T- lymphocytes and B-lymphocytes to both mitogenic and allospecific stimulation. MPA has potent cytostatic effects on lymphocytes and 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. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 and 2, but did block the coupling of these events to DNA synthesis and proliferation.

2.2. Pharmacokinetic Properties

Absorption: It is rapidly absorbed after oral administration and hydrolyzed to form of active metabolite MPA. Mycophenolate mofetil concentration is below the limit of quantitation (0.4 µg/mL) and mean absolute bioavailability of AUC 94%. The plasma AUC for MPA appears to increase in a dose proportional fashion in renal transplant patients. MPA Cmax decreases by 40% in patients in presence of food.

Distribution: The apparent volume of distribution of MPA is approximately mean (S.D) 4.0 (±1.2) L/kg. A relevant concentration of MPA bound to plasma albumin is 97%. MPAG bound to plasma albumin is 82%. The binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding.

Metabolism and Excretion: Mycophenolate mofetil undergoes complete metabolism to MPA (mycophnololic acid) presystemically after oral dosing. The active metabolite, MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is pharmacologically inactive. Radiolabeled mycophenolate mofetil resulted in complete recovery of drug (93%) in urine and (6%) in feces. Most of the dose is excreted in the urine as MPAG. The metabolites moiety is also recovered in the urine.

2.3. Preclinical Safety Data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or Cmax) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or Cmax) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day. Two genotoxicity assays (in vitro mouse lymphoma assay and in vivo mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells.

Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity. Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients.

In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation. In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity.
The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients.

Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure).

The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials, which now provide safety data of more relevance to the patient population.

6. Pharmaceutical Particulars

1. List of Excipients

Microcrystalline Cellulose (Plain)
Hydroxy Propyl Cellulose (Klucel -HXF)
Povidone (PVPK-90)
Croscarmellose Sodium
Microcrystalline Cellulose (PH 102)
Purified Talc
Magnesium Stearate
Purified Water

Composition of Film Coat Universal (FCAQ4508)
Hydroxy Propyl Methyl Cellulose
Hydroxy Propyl Cellulose
Polyethylene Glycol
Talc
Titanium Dioxide
Iron Oxide Red
Iron Oxide Black
Lake of Ponceau 4R

2. Incompatibilities

Not applicable

3. Shelf Life

36. Months

6.4 *Special Precaution for storage*

Do not store above 30°C. Protect from light.

5. Nature and Contents of Container

10 tablets are packed in Alu-PVDC blister pack. Such 1 blister pack is packed in a printed carton with packing insert.

6. Special precaution for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder and Manufacturing Site Addresses

Name and Address of Marketing Authorization Holder
Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
E-mail: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
E-mail: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number
TAN 22 HM 0141

9. Date of First <Registration> / Renewal of The <Registration>
13/04/2022

10. Date of Revision of the Text