BIOS LAB PVT.LTD.

B8, MILAN COMPLEX,SARKHEJ,AHMEDABAD.
QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS FOR FINISHED PRODUCT

GENERIC NAME	Myophnolate Mofetil Tablets I.P. 500 mg		
PRODUCT NAME	BIO MMF TABLETS	**Report No.**	TF - 200042
Mfg by / Supplied by	RIVPRA FORMULATION PVT LTD	**Batch No.**	T-1912236
Marketed by	BIOS LAB PVT LTD.	**Batch Size**	30,000 TABS
Mfg Date	12/2019	**Exp Date**	11/2021
Date of receiving	07-01-2020	**Date of Completion**	11-01-2020
Sample Qty	40 tabs	**Mfg Lic No**	35/UA/2008

TEST	**RESULT**	**SPECIFICATION**
Description	Brick Red coloured elongated biconvex film coated tablets having scored on one side	Brick Red coloured elongated biconvex film coated tablets having scored on one side
Identification (A) :-	Complies	When examined in the range 200 nm to 400 nm, the solution obtained in the dissolution test shows as absorption maxima and minima at the same wavelenghth +- 3 as that of reference Solution of mycophenolate moftil prepared in the same manner.
(B) :-	Complies	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay
Average weight	718.97 mg	718.0 mg +- 5 %
Uniformity of Weight	+0.88% to -0.81%	+-5%
Disintegration time/Dissoltion	84.52% to 89.28%	D. NLT 70.0% in 5 min
	95.63% to 99.60%	NLT 85.0% in 15 min
Related substances		
Mycophenolic acid	0.21%	NMT 1.0%
Mycophenolate N-oxide analog	0.065%	NMT 0.2%
Any other impurity	0.031%	NMT 0.1%
Total impurities	0.21%	NMT 1.5%
Dimension	Length 17.25 mm	17.10 mm +- 0.2 mm
	Width 8.18 mm	8.10 mm +- 0.2 mm
	Thickness 5.56 mm	5.70 mm +- 0.3 mm
Assay	Each film coated tablet on average contains :-	

Ingredients	**Obtained**	**Percent**	**Claim**	**LIMIT**	**METHOD**
Mycophenolate Mofetil I.P.	504.32 mg	100.86%	500.0 mg	470.0 to 525.0 mg	IP

BIO-MMF™

Each film coated tablet contains

Mycophenolate mofetil – 500 mg
Excipients …….. q.s.

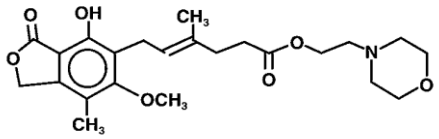
WARNING

Embryofoetal Toxicity, Malignancies and Serious Infections,
Female users of childbearing potential must use contraception. Use of BIO-MMF™ during pregnancy is associated with increased risk of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention.

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 BIO-MMF™. 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.

PHARMACEUTICAL DESCRIPTION

BIO-MMF™ (Mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl(E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzof uranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50g/mol and the following structural formula:



Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43µg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238.
The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

PHARMACOLOGY

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA 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 more potent cytostatic effects on lymphocytes than on other cells.

MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. 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. Mycophenolate mofetil did 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 did block the coupling of these events to DNA synthesis and proliferation.

Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of Mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} 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. MPA at clinically relevant concentrations is 97% bound to plasma albumin.

Metabolism

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).

Excretion

A negligible amount of substance is excreted as MPA (< 1% of dose) in the urine. Oral administration of radio labeled mycophenolate mofetil results in complete recovery of the administered dose with 93% of the administered dose recovered in the urine and 6% recovered in the feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, 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 (see **OVERDOSAGE**).

SPECIAL POPULATIONS

Renal Impairment

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 m^2) were 28–75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3–6 folds higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Hepatic Impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Pediatrics

Pharmacokinetic parameters were evaluated in 59 paediatric renal transplant patients (aged 2 to 18 years) given 500 mg/m^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving BIO-MMF™ 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.

Gender

Data obtained from several studies were pooled to look at any gender- related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose).

Geriatrics

Pharmacokinetic behavior of BIO-MMF™ in the elderly (≥ 65 years) has not been formally evaluated.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA AUC (0–12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2–3 folds higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of BIO-MMF™ does not appear to be necessary.

Patients taking oral contraceptives

The pharmacokinetics of oral contraceptives were unaffected by co-administration of BIO-MMF™. A study of the co-administration of BIO-MMF™ (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 nontransplant women (not taking other immunosupressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of BIO-MMF™ on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

INDICATIONS

Renal, Cardiac, and Hepatic Transplant

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

CONTRAINDICATIONS

Allergic reactions to Mycophenolate mofetil have been observed; therefore, Mycophenolate mofetil is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. It is also contraindicated in pregnancy or breast feeding.

WARNINGS AND PRECAUTIONS

WARNINGS

(See boxed WARNING) Lymphoma and Malignancy

Patients receiving immunosuppressive regimens involving combinations of drugs, including BIO-MMF™, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disease or lymphoma developed in minor cases of patients receiving BIO-MMF™ (2 g or 3 g) with other immunosuppressive agents of renal, cardiac, and hepatic transplant patients.

In pediatric patients, no other malignancies besides lymphoproliferative disorder have been observed.

Combination with Other Immunosuppressive Agents

BIO-MMF™ has been administered in combination with antithymocyte globulin, OKT3, cyclosporine and corticosteroids. The efficacy and safety of the use of BIO-MMF™ in combination with other immunosuppressive agents have not been determined.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with Mycophenolate mofetil. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function. 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.

Neutropenia

Patients receiving mycophenolate mofetil should be monitored for neutropenia. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of renal, cardiac, and hepatic rejection.

Patients receiving BIO-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 (PRCA)

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with BIO-MMF™ in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil 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 BIO-MMF™ therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

PRECAUTIONS

General

Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with BIO-MMF™ 3 g daily. In pediatric renal transplant patients, in minor cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving BIO-MMF™ were also receiving other drugs known to be associated with these complications. BIO-MMF™ has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, BIO-MMF™ should be administered with caution in patients with active serious digestive system disease.

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. BIO-MMF™ may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function post-transplant, mean MPA AUC (0-12h) was comparable, but MPAG AUC (0-12h) was 2-fold to 3-fold higher, compared to that seen in post-transplant patients without delayed renal graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, and hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving BIO-MMF™ than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with BIO-MMF™ than in that receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with BIO-MMF™.

There were more herpes virus (H. simplex, H. zoster, and cytomegalovirus) infections in cardiac transplant patients treated with BIO-MMF™ compared to those treated with azathioprine. It is recommended that BIO-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.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of BIO-MMF™ with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of BIO-MMF™ (see **PRECAUTIONS: Drug Interactions**).

On theoretical grounds, BIO-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.

During treatment with BIO-MMF™, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: Drug Interactions: Live Vaccines**).

Information for Patients

- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking BIO-MMF™.
- Inform women of childbearing potential that use of BIO-MMF™ in pregnancy is associated with an increased risk of first trimester pregnancy loss and an

increased risk of birth defects, and that they must use effective contraception.

- Discuss pregnancy plans with female patients of childbearing potential.
    - Any female of childbearing potential must use highly effective (two methods) contraception 4 weeks prior to starting BIO-MMF™ therapy and continue contraception until 6 weeks after stopping BIO-MMF™ treatment, unless abstinence is the chosen method (see **WARNINGS: Pregnancy**).
    - A patient who is planning a pregnancy should not use BIO-MMF™ unless she cannot be successfully treated with other immunosuppressant drugs.

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 (see **WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

DRUG INTERACTIONS

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. Mycophenolate mofetil has not been administered concomitantly with azathioprine.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant ciclosporin treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with Mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of Mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which do not interfere with MPA´s enterohepatic cycle.

Telmisartan

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

Acyclovir

Co-administration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy

volunteers resulted in no significant change in MPA AUC and C_{max}. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. 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.

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 increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and Mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom Mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co-administration of Mycophenolate mofetil. BIO-MMF™ may not have any influence on the ovulation suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives are co-administered with BIO-MMF™ with caution and additional birth control methods be considered (see **WARNINGS: Pregnancy**).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of Mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC 0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust Mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly. BIO-MMF™ is not recommended to be given with rifampicin concomitantly unless the benefit outweighs the risk.

Sevelamer

Decrease in MPA C_{max} and AUC (0-12) by 30% and 25%, respectively, were observe when Mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). 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.

Trimethoprim/Sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Norfloxacin and Metronidazole

In healthy volunteers, no significant interaction was observed. Mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of Mycophenolate mofetil.

Ciprofloxacin and Amoxicillin plus Clavulanic acid

Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction.

However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tacrolimus

In hepatic transplant patients initiated on Mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of Mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of Mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by Mycophenolate mofetil.

Antacids with Magnesium and Aluminum Hydroxides

BIO-MMF™ may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that BIO-MMF™ and the antacid not be administered simultaneously.

Cholestyramine

BIO-MMF™ is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Other interactions

Co-administration of probenicid with mycophenolate mofetil raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

Increased Susceptibility to Infection and the Possible Development of Lymphoma

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimize the risk for skin cancer, exposure to

sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as bacterial, fungal, viral and protozoal, fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML)

Hypogammaglobulinaemia

BIO-MMF™ in combination with other immunosuppressant have caused hypogammaglobulinaemia in association with recurrent infections Patients on Mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with BIO-MMF™ 3 g daily. In paediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed. Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage, and perforation, Mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.

Bronchiectasis

There have been published reports of bronchiectasis in adults and children who received Mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching Mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

HGPRT Deficiency

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.

Pure Red Cell Aplasia (PRCA)

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with

Mycophenolate mofetil in combination with other immunosuppressants.

Concomitant Medications

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. Caution should be used in the concomitant administration of BIO-MMF™ with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate mofetil.

Vaccination

The use of live vaccines should be avoided patients with an impaired immune response. The antibody response to other vaccines may be diminished. During treatment with BIO-MMF™, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: General**). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Renal Impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml•min-1•1.73 m-2), outside the immediate post-transplant period, doses > 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.

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.

PREGNANCY

Teratogenic Effects: Pregnancy Category D

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. 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.

It is recommended that Mycophenolate mofetil therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate mofetil therapy, during therapy, and for six weeks following discontinuation of therapy.

The use of Mycophenolate mofetil is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. It should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus. Patients should be instructed to consult their physician immediately should pregnancy occur.

Lactation

Mycophenolate mofetil is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, Mycophenolate mofetil is contraindicated in nursing mothers.

Nursing Mothers

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.

Pediatric Use

Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.

Geriatric Use

As per clinical experience there are 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.

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.

Treatment during rejection of 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 mycophenolate mofetil dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

ADVERSE REACTIONS

Adverse reactions associated with the administration of Mycophenolate mofetil in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections.

There are increased risk of developing lymphomas and other malignancies, particularly of the skin. Lymphoproliferative disease or lymphoma developed in 0.6% of patients receiving Mycophenolate mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g, data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6% of patients; other types of malignancy occurred in 1.1% of patients.

The most common opportunistic infections in patients receiving Mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year

were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%.

Blood and lymphatic system disorders

- Very common: Leucopenia, thrombocytopenia, anaemia
- Common: Pancytopenia, leucocytosis

Metabolism and nutrition disorders

- Common: Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia.

Psychiatric disorders

- Common: Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia

Nervous system disorders

- Common: Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia

Cardiac Disorders

- Common: Tachycardia

Vascular Disorders

- Common: Hypotension, hypertension, vasodilatation

Respiratory, thoracic and mediastinal Disorders

- Common: Pleural effusion, dyspnoea, cough

Skin and subcutaneous tissue disorders

- Common: Skin hypertrophy, rash, acne, alopecia,

Musculoskeletal and connective Tissue disorders

- Common: Arthralgia

The principal adverse reactions associated with the administration of BIO-MMF™ include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection (see **WARNINGS: Infections** and **WARNINGS: Progressive Multifocal Leukoencephalopathy (PML)**).

POSTMARKETING EXPERIENCE

Congenital Disorders: Congenital malformations including ear malformations have been reported in offspring of patients exposed to mycophenolate mofetil during pregnancy.

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Hematologic and Lymphatic: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with BIO-MMF™ in combination with other immunosuppressive agents.

Resistance Mechanism Disorders: 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. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with BIO-MMF™. The reported

cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post-transplant patients receiving BIO-MMF™.

If you experience any side-effects, talk to your doctor or pharmacist or write to info@bioslab.co.in
By reporting side-effects, you can help provide more information on the safety of this product.

OVERDOSAGE

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases, no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the medicinal product.
It is expected that an overdose of mycophenolate mofetil could possibly result in 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.
Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic re-circulation of the drug.
The experience with overdose of BIO-MMF™ in humans is very limited. The events received from reports of overdose fall within the known safety profile of the drug. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

DOSAGE AND ADMINISTRATION

The amount you take depends on the type of transplant you have had. This medicine is taken orally. The usual doses are shown below. Treatment will continue for as long as you need to prevent you from rejecting your transplant organ.

General Dosing Guidance for Renal Transplant Patients

Adults

The first dose is given within 72 hours of the transplant operation.
The daily dose is 4 tablets (2 g of the medicine) taken as 2 separate doses. Take 2 tablets in the morning and then 2 tablets in the evening.

Children (aged 2 to 18 years)

The dose given will vary depending on the size of the child.

Your doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m^2"). The recommended dose is 600 mg/ m^2 taken twice a day (up to a maximum of 2 g daily).

Children (< 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.

General Dosing Guidance for Cardiac Transplant Patients

Adults

The first dose is given within 5 days of the transplant operation.

The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses. Take 3 tablets in the morning and then 3 tablets in the evening.

Children

There is no information for the use of mycophenolate mofetil in children with a heart transplant.

General Dosing Guidance for Hepatic Transplant Patients

Adults

The first dose of oral Mycophenolate mofetil will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.

The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses Take 3 tablets in the morning and then 3 tablets in the evening.

Children

There is no information for the use of mycophenolate mofetil in children with a liver transplant.

Geriatrics

The recommended oral dose of 1 g bid for renal transplant patients, 1.5 g bid for cardiac transplant patients, and 1 g bid administered intravenously or 1.5 g bid administered orally in hepatic transplant patients is appropriate for elderly patients (see **PRECAUTIONS: Geriatric Use**).

SHELF LIFE

Please see Manufacturing date and Expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

INCOMPATIBILITY: None

STORAGE CONDITION:

- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

- Keep out of reach of children.
- BIO-MMF™ should not be used after the date marked "EXP" on the pack.

MEDICATION GUIDE

Read the Medication Guide that comes with BIO-MMF™ before you start taking it and each time you refill your prescription. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

GENERAL INFORMATION ABOUT BIO-MMF™

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BIO-MMF™ for a condition for which it was not prescribed. Do not give BIO-MMF™ to other people, even if they have the same symptoms that you have. It may harm them. This Medication Guide summarizes the most important information about BIO-MMF™. If you would like more information, talk with your doctor.

PRESENTATION: Mycophenolate mofetil – 500 mg Tablets

PACKING: 1*10 TAB

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