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

Biocon

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Mycophenolate Mofetil Tablets IP 500 mg

PSIEN® 500 सीएन ५००

COMPOSITION:
Each film coated tablet contains:
Mycophenolate Mofetil IP 500 mg
Excipients q.s.
Colours: Ferric Oxide Red USP NF, Ferric Oxide Black USP NF & Titanium Dioxide IP

WARNING

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use Mycophenolate mofetil. Patients receiving Mycophenolate mofetil 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.

Female users of childbearing potential must use contraception. Use of Mycophenolate mofetil during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

DESCRIPTION
PSIEN® 500 (Mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor used to prevent rejection in allogenic organ transplant.

The chemical name for Mycophenolate Mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, and a molecular weight of 433.50,

ATC code: L04AA06

CLINICAL PHARMACOLOGY
Mechanism of Action
Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. 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 potent cytostatic effects on lymphocytes. 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.

Pharmacokinetics
Following oral administration, Mycophenolate Mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active.

Absorption
In healthy volunteers, the mean absolute bioavailability of oral Mycophenolate Mofetil was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of Mycophenolate Mofetil up to a daily dose of 3 g. Food had no effect on the extent of absorption of Mycophenolate Mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA Cmax was decreased by 40% in the presence of food

Distribution
The mean (± SD) apparent volume of distribution of MPA in healthy volunteers is approximately 4.0 (± 1.2) L/kg following oral administration. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed renal graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

Metabolism
Following oral Mycophenolate Mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically 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. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of Mycophenolate Mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine. Increased plasma concentrations of Mycophenolate Mofetil metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency.

Excretion
Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled Mycophenolate Mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in 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 (>100µg/ml) small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug. Mean apparent half-life and plasma clearance of MPA are 17.9 ± 6.5 hours and 193 ± 48 mL/min following oral administration.

INDICATIONS
PSIEN® 500 is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. PSIEN® 500 should be used concomitantly with other immunosuppressants and corticosteroids.

CONTRAINDICATIONS
PSIEN® 500 is contraindicated in patients with a hypersensitivity to Mycophenolate Mofetil, mycophenolic acid or any component of the drug product

WARNINGS
Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolate mofetil, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. 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. Over suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

It is recommended that Mycophenolate mofetil therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate mofetil therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see PRECAUTIONS: Pregnancy).

Severe neutropenia [absolute neutrophil count (ANC) <0.5 x 103/µ L] developed in up to 2.0% of renal patients receiving Mycophenolate mofetil 3 g daily. Patients receiving Mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to Mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC <1.3 x 103/µ L), dosing with Mycophenolate mofetil should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. 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 Mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

PRECAUTIONS
General
Mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.

Doses of Mycophenolate mofetil greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed

It is recommended that Mycophenolate mofetil should 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 Mycophenolate mofetil with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate mofetil.

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 (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
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.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week oral carcinogenicity study in mice, Mycophenolate Mofetil in daily doses up to 180

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mg/kg was not tumorigenic. The genotoxic potential of Mycophenolate Mofetil was determined in five assays. Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay and the in vivo mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients when corrected for BSA.

Pregnancy
Category D - Use of Mycophenolate mofetil during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. Mycophenolate mofetil should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning Mycophenolate mofetil therapy, during therapy and for 6 weeks after Mycophenolate mofetil has been stopped.

Nursing Mothers
Studies in rats have shown Mycophenolate Mofetil to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mycophenolate Mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use
Reported clinical experience has not identified differences in responses between the elderly and younger patients

DRUG – DRUG INTERACTIONS
It is recommended that Mycophenolate mofetil not be administered concomitantly with azathioprine or other immunosuppressant because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

Antivirals like acyclovir/ Ganciclovir compete for tubular secretion, further increasing the concentrations of both drugs.

In view of potential to reduce the efficacy of Mycophenolate mofetil drugs that interfere with enterohepatic recirculation like cholestyramine/ colestipol, caution should be used in the concomitant administration of these drugs with Mycophenolate mofetil.

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. Concomittant administration of antacids or iron salts (eg, ferrous sulfate) because they may decrease Mycophenolate mofetil effectiveness. Mycophenolate mofetil may decrease the effectiveness of Oral contraceptives.

The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with Mycophenolate Mofetil in monkeys 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.

SIDE EFFECTS
The principal adverse reactions associated with the administration of Mycophenolate mofetil include diarrhoea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection
The following adverse events were reported with 3% to <20% incidence in renal, cardiac, and hepatic transplant patients treated with Mycophenolate mofetil, in combination with Cyclosporine and Corticosteroids.
General : abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis

Hematological: coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.
Urogenital: acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis, nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder.

Cardiovascular: angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased.
Metabolic and Nutritional: abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss

Digestive: anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis

Respiratory: apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration

Nervous system: agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertonia, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo

Skin and appendages: acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash.

Endocrine: Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder

Musculoskeletal: arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis

Special senses: abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder

OVER DOSAGE
The experience with overdose of Mycophenolate mofetil in humans is very limited. The highest dose administered to renal transplant patients in clinical trials has been 4 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 diarrhoea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100µg/ml), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine

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 renal transplant patients.

Storage
Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

Shelf Life: Please refer Blister/Carton.

Presentation
PSIEN® 500 is available in 10 tablets per blister

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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BF/LL/3705/01

Leaflet revised on August 2019

To report adverse events and/or product complaints visit our website www.biocon.com or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**